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In association with the British Cardiac Society

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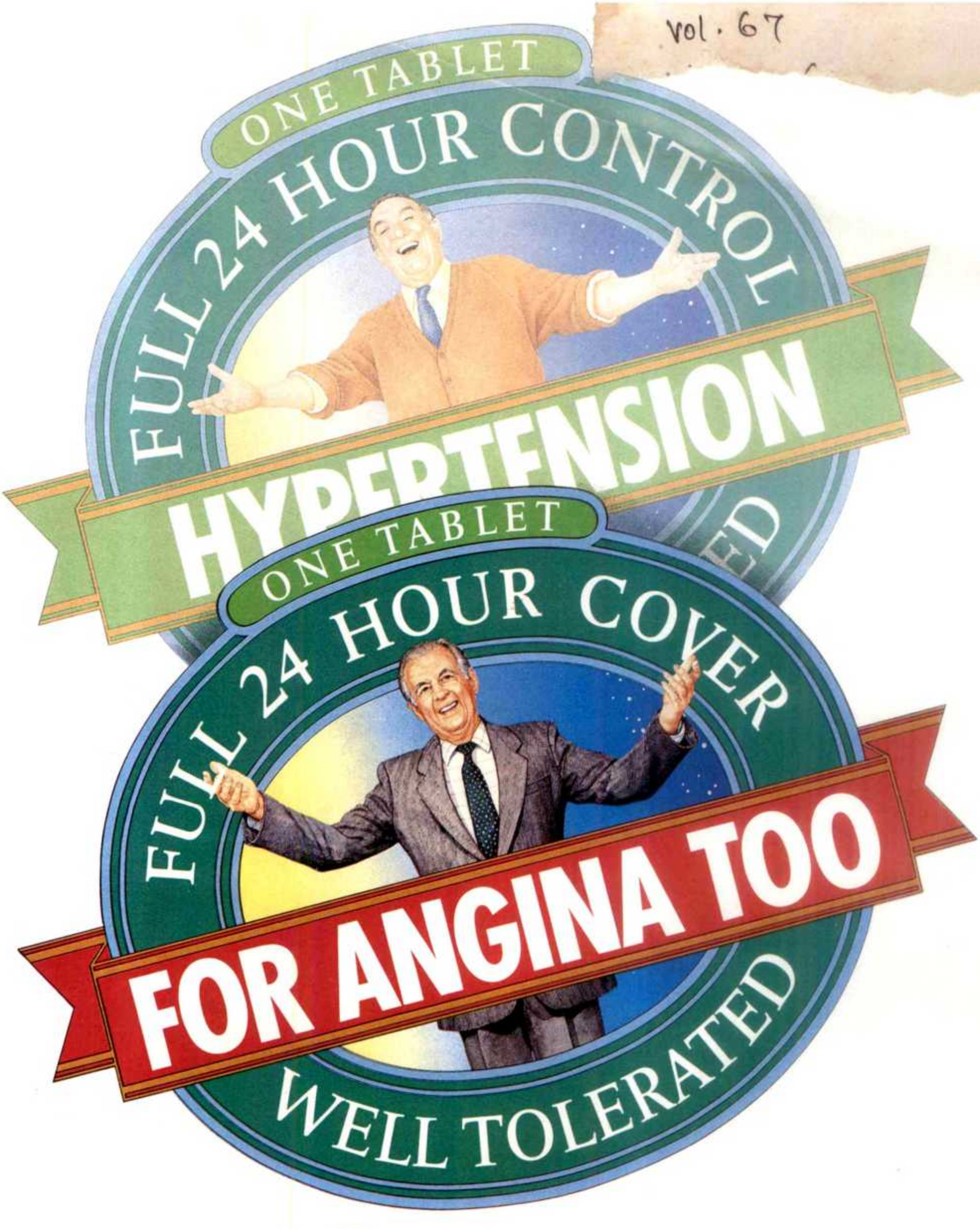

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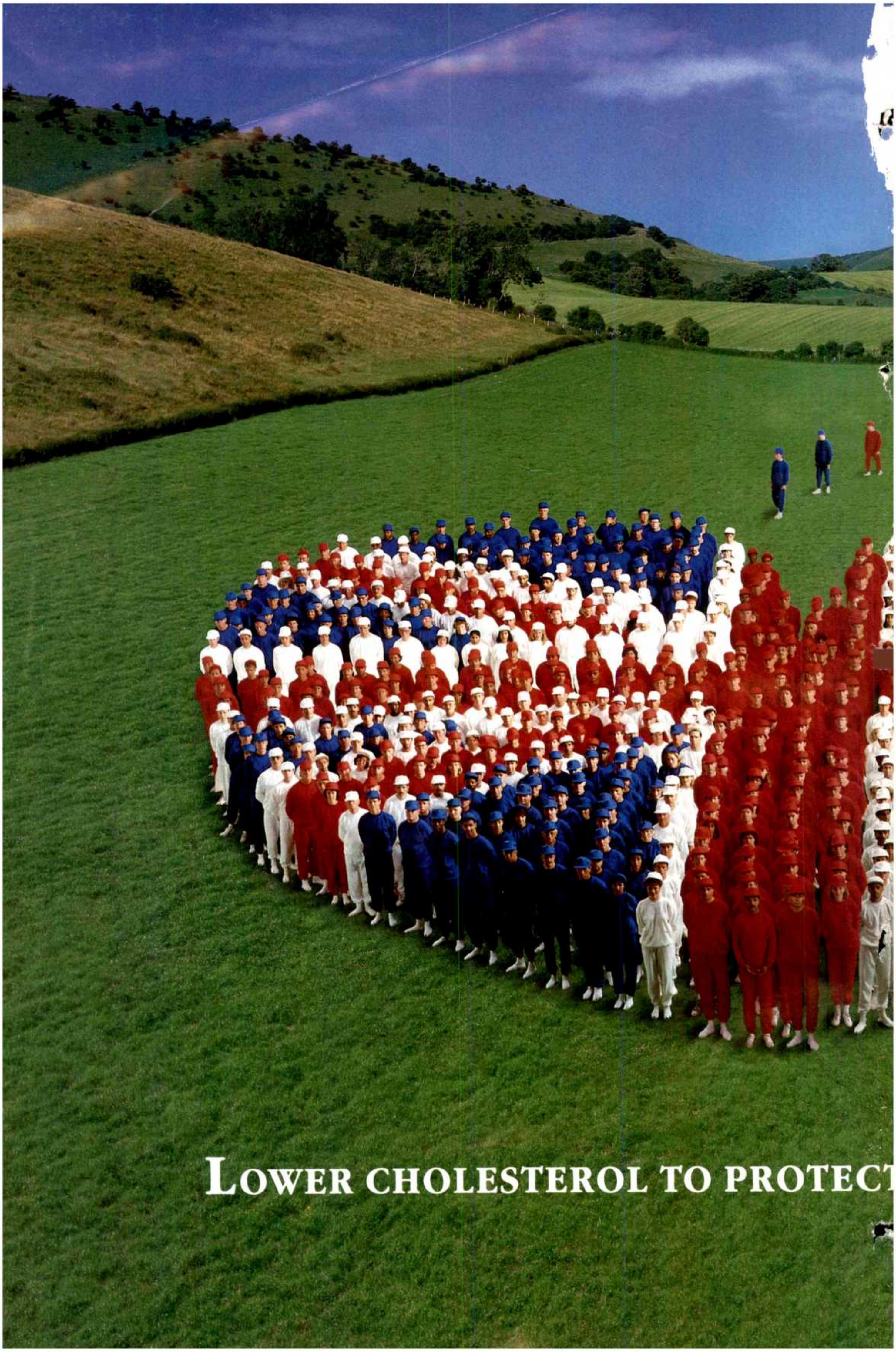
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REFERENCES

1. OPCS Monitor DH2. June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

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Editorials

Torsade de pointes: chaos, sixteen years on?

As early as 1923 it was recognised that quinidine could cause sudden death,[1] but it was not until 1964 that the cause of quinidine syncope was unequivocally established as a form of paroxysmal ventricular arrhythmia.[2] In 1966 Dessertenne of Paris reported his fundamental observations on the characteristics of the arrhythmia and proposed the term torsade de pointes.[3] (Even now there is inconsistency in French publications about the plural usage.) He noted an association with bradycardia and that quinidine and similar antiarrhythmic drugs could induce the arrhythmia and were associated with a high mortality when used for its management. The arrhythmia seemed to be an idiosyncratic reaction to therapeutic or sub-therapeutic doses of the drug and not a manifestation of toxicity.

Although it is 16 years since the *British Heart Journal* first drew the attention of English speaking cardiologists to torsade de pointes,[4] it had been briefly discussed two years earlier[5]; indeed, while isolated instances of this arrhythmia had been reported previously in English language journals, its nature and the circumstances surrounding its occurrence had been poorly described. This is no longer the case and there are now extensive publications from many countries. Effective treatment is available for most varieties of this condition, but it is not clear that the clinical recognition of the arrhythmia, and therefore its management, has generally improved. Although understanding of the arrhythmia at a practical, clinical level has increased, the basic electrophysiological mechanisms underlying torsade de pointes remain obscure despite a decade and a half of research.

Definition and diagnosis

The essential features of the diagnosis are of a variant of paroxysmal ventricular tachycardia associated with prolongation of the QT interval (more accurately the JT interval) or prominent U waves[3] which may be hard to distinguish from the end of a long T wave.[6] However, QT prolongation or U waves may appear only briefly before the onset of the arrhythmia. Typically the QRS axis changes direction in an undulating fashion during paroxysms. Occasionally paroxysms appear uniform. Episodes may be brief, consisting of only a few complexes, or prolonged when they may degenerate into ventricular fibrillation. Between episodes pauses are also often observed on the electrocardiogram.[3]

Underlying mechanisms of arrhythmia

Clinically, torsade de pointes is a heterogeneous condition and there is no reason why the basic mechanisms underlying the arrhythmia might not also vary. However, there are several unifying features on the electrocardiogram that suggest that a common substrate may exist.

The response to sympathetic stimuli identifies two main types of torsade de pointes. One is associated with bradycardia and ventricular pauses and improves with sympathetic stimulation, which increases the ventricular rate. This form tends to occur in older patients who are more likely to have conduction defects and perhaps also to receive antiarrhythmic agents. The other is precipitated by increased sympathetic activity. This tends to occur in younger subjects and is sometimes associated with sensorineural deafness.[7 8] Episodes of bradycardia may also be seen between events in these patients.

Possible role of reentry

The propagation of the activation wavefront, the action potential duration, and the process of repolarisation are asynchronous events. There are several gradients within the heart, with the time for repolarisation being shorter near the apex than near the base and shorter near the epicardium than near the endocardium, which accounts for the fact that QRS and T wave polarity are usually the same.[9] The QT interval encompasses the time from first activation of the ventricular myocardium to the final repolarisation. Thus the QT interval may be prolonged if any of the above three phases is delayed. Regional changes in the above events will lead to regional variations (dispersion) in the refractory period, predisposing to reentry arrhythmias. Such arrhythmias may propagate in irregular patterns as areas with prolonged refractory periods are encountered which act as shifting inexcitable island barriers to the progress of ventricular activation. Both bradycardia and quinidine-like agents can exacerbate the heterogeneity of repolarisation and increase the likelihood of reentrant arrhythmias.[10] However, if torsade de pointes were due to reentry a sustained ventricular tachycardia of this type should be inducible by an electrical stimulus during the TU wave, which was not the case at least in our early experience,[11] and subsequently that of others. This is strong evidence against the reentry theory.

Possible role of "chaotic" behaviour

More recently, chaos theory has been applied to the study of ventricular arrhythmias. In common parlance chaos refers to disorder. However, scientists have appropriated the term to indicate the underlying orderliness of apparent disorder.[12] Thus true random "noise" in any system is not "chaos". In the dynamics of chaos, two initial conditions that are very similar will eventually behave very differently as time proceeds owing to subtle interactions with their environments. There are definite rules underlying this process, which can be detected and defined by mathematical equations.

The reason for alterations in a stable heart rhythm might be changes in electrolyte concentrations, variations in autonomic tone, or myocardial ischaemia. Any of these perturbations will alter the behaviour of the myocardium and the conduction system and will also have effects on other systems that modulate cardiac activity. Ultimately the perturbation will feed back on itself (reinforcing or diminishing the effects of the original intervention), closing the loop. For instance, myocardial ischaemia may lead to increased sympathetic activity and hence an increase in heart rate and contractility which in turn may aggravate the ischaemia. At the moment chaos theory is largely concerned with detecting the presence of such interactions but has not advanced far enough to predict the outcome.

In torsade de pointes, ventricular pauses or imbalances in autonomic tone could act as perturbations in a normally stable rhythm. Although models of torsade de pointes have not been studied specifically for evidence of chaos, ventricular tachycardia and fibrillation have.[13] In these models there is evidence of chaotic behaviour before the appearance of ventricular fibrillation, but ventricular fibrillation was not itself thought to be chaotic. The perturbations which might lead to chaos in these models also lead to an ideal substrate for reentry arrhythmias, and these, rather than a true chaotic system, seem responsible for ventricular tachycardia and its degeneration to fibrillation.

Chaos in the technical sense is not necessarily unstable, and indeed it is likely that chaos is a healthy state in most biological systems.[14] For instance the heart rate varies continually under the influence of the autonomic nervous system which itself changes the input to the heart according to various factors including the level of mental, emotional, and physical activity; respiratory phase; and blood pressure. When cardiac disease supervenes (for example, heart failure) the heart rate becomes fixed, the normal chaotic behaviour is lost, and the risk of sudden cardiac death increases.[15]

Possible role of early afterdepolarisations

As defined by Cranefield and Aronson,[16] an early afterdepolarisation is a depolarising afterpotential that begins before repolarisation would normally be complete. Lately, the idea that the U waves represent early afterdepolarisations has gained ground.[17] At the cellular level the rate of repolarisation depends on the rapidity with which potassium is ejected from the cell, which far outweighs the usual slower continued influx of calcium and sodium.[18] However, if the egress of potassium is slowed or halted,[18 19] the inward flow of calcium and sodium will slow or reverse the normal repolarisation of the cell thus producing early afterdepolarisations. If the early afterdepolarisations are sufficiently large they may trigger further action potentials and themselves lead to the production of arrhythmias. Caesium by blocking potassium repolarising currents can provoke early afterdepolarisations, QT(U) abnormalities, and arrhythmias and thus produce a condition identical with torsade de pointes.[20]

Several observations on the clinical setting of torsade de pointes support a role for early afterdepolarisations. Electrolyte disturbances can cause prolongation of the QT interval. Hypokalaemia and hypomagnesaemia both increase the QT(U) interval and early afterdepolarisations and may provoke torsade de pointes, while magnesium given intravenously may suppress torsade de pointes even in the absence of hypomagnesaemia.[21] Indeed, a case of what was clearly torsade de pointes responding promptly to parenteral magnesium was reported over 50 years ago.[22] However, acute potassium supplementation does not seem to be effective even when the serum potassium is low.[23] Hypocalcaemia causes QT prolongation, mainly by increasing ST segment prolongation rather than TU wave prolongation, and it has not been implicated as a cause of torsade de pointes.[24] Bradycardia provokes early afterdepolarisations, especially in the presence of low extracellular potassium concentrations and in the presence of low concentrations of quinidine.[18] Bradycardia may facilitate a hypokalaemic micro-environment around the cell because a prolonged diastole would allow the sodium/potassium pump to operate for an extended period. Caesium blocks potassium channels during the repolarisation phase of the action potential and can accentuate early afterdepolarisations and provoke arrhythmias.[25] This is especially likely if the sodium channel has not been blocked by tetrodoxin.

Sympathetic stimuli can increase not only late but also early afterdepolarisations in animal models of torsade de pointes,[26 27] probably by enhancing inward sodium and calcium currents during repolarisation or by inducing local hypokalaemia by stimulating cellular potassium uptake. The occurrence of familial forms of the disease, often associated with sensorineural deafness, fits better with a general disturbance of cardiac myocyte function rather than a reentry mechanism.[28] Patients susceptible to torsade de pointes due to one class of quinidine-like antiarrhythmic agents may develop torsade de pointes when given another such agent. Occurrence of torsade de pointes with the related antimicrobial agents erythromycin and pentamidine[29 30] (the latter now used for complications of AIDS) further supports a generalised disturbance of cell function.

Our understanding of torsade de pointes has expanded considerably over the past 16 years. Basic science has developed models of the condition that reveal the underlying electrophysiological disorder which might help predict the likely effect of new drugs.

Although the direct experimental evidence is not conclusive the circumstantial clinical evidence points strongly towards a role for early afterdepolarisations in the genesis of torsade de pointes, which may not be so far from Dessertenne's original theory of alternating ventricular foci. Indeed, Dessertenne may have coined what is now a relevant phrase with his reference to "order and chaos in electrocardiography".[31]

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1 Viko LE, Marvin HM, White PD. Clinical report of the use of quinidine sulfate. *Arch Intern Med* 1923;31:345–63.
2 Selzer A, Wray WH. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation* 1964;30:17–26.
3 Dessertenne F. La tachycardie ventriculaire à deux foyers opposés variables. *Arch Mal Coeur* 1966;59:263–72.
4 Krikler DM, Curry PVL. *Torsade de pointes,* an atypical ventricular tachycardia. *Br Heart J* 1976;38:117–20.
5 Krikler DM. A fresh look at cardiac arrhythmias. Pathogenesis and presentation. *Lancet* 1974;i:913–8.
6 Ejvinsson G, Orinius E. Prodromal ventricular premature beats preceded by a diastolic wave. *Acta Med Scand* 1980;208:445–50.
7 Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT-interval, and sudden death. *Am Heart J* 1957;54:59–68.
8 Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1975;89:378–90.
9 Burgess MJ, Green LS, Millar K, *et al.* The sequence of normal ventricular recovery. *Am Heart J* 1972;84:660–9.

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10 Han J, Millet D, Chizzonitti B, Moe GK. Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. *Am Heart J* 1966;71:481–7.
11 Evans TR, Curry PVL, Fitchett DH, Krikler DM. "Torsade de pointes" initiated by electrical ventricular stimulation. *J Electrocardiol* 1976;9: 255–8.
12 Gleick J. *Chaos: making a new science*. New York: Viking Penguin, 1987.
13 Kaplan DT, Cohen RJ. Is fibrillation chaos? *Circ Res* 1990;67:886–92.
14 Winfree AT. Sudden cardiac death: a problem in topology. *Sci Am* 1983; 248:118–31.
15 Goldberger AL. Non-linear dynamics in heart failure: implications of long-wavelength cardiopulmonary oscillations. *Am Heart J* 1984;107:612–5.
16 Cranefield PF, Aronson RS. *Cardiac arrhythmias: the role of triggered activity and other mechanisms*. New York: Futura Publishing, 1988:12.
17 El-Sherif N, Bekheit SS, Henkin R. Quinidine-induced long QTU interval and torsade de pointes: role of bradycardia-dependent early afterdepolarisations. *J Am Coll Cardiol* 1989;14:252–7.
18 Roden DM, Hoffman BF. Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. *Circ Res* 1985;56: 857–67.
19 Corabeouf E, Deroubaix E, Coulombe A. Acidosis induced abnormal repolarizations and repetitive activity in isolated dog Purkinje fibres. *J Physiol (Paris)* 1980;76:97–106.
20 Levine JW, Spear JF, Guanieri T, *et al*. Cesium chloride-induced long QT syndrome: demonstration of afterdepolarisations and triggered activity in vivo. *Circulation* 1985;72:1092–103.
21 Tzivoni D, Keren A, Cohen AM, *et al*. Magnesium therapy for torsade de pointes. *Am J Cardiol* 1984;53:528–30.
22 Zwillinger L. Ueber die Magnesiumwirkung auf das Herz. *Klin Wochenschr* 1935;14:1429–33.
23 Khan MM, Logan KR, McComb JM, Adgey AAJ. Management of recurrent ventricular tachyarrhythmias associated with QT prolongation. *Am J Cardiol* 1981;47:1301–8.
24 Bronsky D, Dubin A, Kushner DS, *et al*. Calcium and the electrocardiogram III. The relationship of the intervals of the electrocardiogram to the levels of serum calcium. *Am J Cardiol* 1961;7:840–3.
25 Brachmann J, Scherlag BJ, Rosenshtraukh LV, Lazzara R. Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. *Circulation* 1983;68:846–56.
26 Hanich RF, Levine JH, Spera JF, Moore EN. Autonomic modulation of ventricular arrhythmia in cesium-chloride-induced long QT syndrome. *Circulation* 1988;77:1149–61.
27 Cranefield PF. Action potentials, after potentials and arrhythmias. *Circ Res* 1977;41:415–23.
28 Weintraub RG, Gow RM, Wilkinson JL. The congenital long QT syndromes in childhood. *J Am Coll Cardiol* 1990;16:674–80.
29 Schoenenberger RA, Haefeli WE, Weiss P, Ritz RF. Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsade de pointes). *BMJ* 1990;300:1375–6.
30 Stein KM, Haronian H, Mensah GA, Acosta A, Jacobs J, Kligfield P. Ventricular tachycardia and torsade de pointes complicating pentamidine therapy of pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Am J Cardiol* 1990;66:888–9.
31 Dessertenne F. Ordre ou chaos en électrocardiographie. *Nouv Presse Méd* 1973;2:1511–2.

Is there chaos in cardiology?

A recent paper stated that "the health care system in the United States is in chaos."[1] Though I am sure readers know what was meant, we have to be careful these days about the definition of chaos. Consulting a medical dictionary is unhelpful because there, chaos (*Pelomyxa carolinensis*) is an amoeba.[2] Descriptions in *Webster*[3] ("a state of things in which chance is supreme . . . nature that is subject to no law . . . a state of utter confusion completely wanting in order, sequence, organisation or predictable operation") do not quite cover the modern, mathematical redefinition of chaos.

The new chaos is characterised by deterministic behaviour, where irregular patterns obey mathematical equations and are critically dependent on initial conditions.[4] Modern chaos theory has been applied to a wide variety of biological phenomena[5] and has become quite fashionable. In certain circles you are regarded as a barbarian if your conversation is not garnished with terms such as Hopf bifurcation points, Liapunov numbers, phase locking, or fractals.

Chaos theory has been used in two areas of cardiac electrophysiology: (*a*) the behaviour of cardiac tissue, or isolated myocytes, during repetitive stimulation and (*b*) fibrillation and prefibrillatory states.

Chaos is irregular behaviour occurring in a nonlinear dynamic system. Cardiac cells may have several nonlinear, time-dependent variables (for instance supernormal excitability) and may exhibit irregular response patterns at a certain stimulation frequency.[6 7] When isolated sheep Purkinje fibres exposed to a solution containing 7 mmol/l K^+ are repetitively stimulated at progressively faster rates, the so-called devil's staircase is seen, where 1:1 responses change into 2:1 and 3:1, with intermediate Wenckebach periodicity between the 1:1 and 2:1, and 2:1 and 3:1 responses. No irregular activity occurs. When, however, the extracellular K^+ concentration is lowered to 4 mmol/l, and the fibres exhibit a brief period of supernormal excitability during the repolarisation phase, deterministic chaotic behaviour occurs at certain cycle lengths: either the stimulus-response pattern shows complex irregularities where no sequence is ever repeated in exactly the same way (this occurs at cycle lengths around 200 ms), or at cycle lengths of 50 ms the relation between cycle length and action potential amplitude is chaotic.[7] This example is chosen to show, on the one hand, that chaotic behaviour can indeed be induced in cardiac tissue, and that some satisfaction can be derived from the consideration that a unifying concept, chaos theory, links the stimulus-response patterns in cardiac cells with other phenomena such as growth during embryonic development[8] or the activity of phrenic nerves during mechanical ventilation of anaesthetised, paralysed cats.[5] On the other hand, the conditions in which chaotic activity arises are extreme: artificial stimulation of isolated tissue at a certain K^+ concentration at unphysiological frequencies.

Can chaotic behaviour be detected in "naturally" occurring rhythms? The obvious candidate for study is ventricular fibrillation, which traditionally has been called chaotic in the Webster sense. The identification of chaos in an existing rhythm is difficult. One technique is power spectrum analysis. A broad-band power spectrum is associated with chaos; however, ordinary random noise has a broad power spectrum as well. The power spectrum of electrocardiographic recordings during ventricular fibrillation is narrow[9 10] and Kaplan and Cohen concluded from their analysis that "there is little utility in classifying fibrillation as chaotic."[10] Would it be useful if fibrillation, or any other rhythm or conduction disorder, could be classified as chaotic? In this respect, the investigators in the chaotic domain are very enthusiastic: "A finding that ventricular fibrillation is chaos would suggest that there is a single mechanism at work in VF, and would provide guidance in the search for clinical precursors of VF";[10] ". . . such new theories may help to strengthen the ties between the basic scientist and the cardiologist by opening new research avenues which may lead to the disclosure of the fundamental mechanisms of severe cardiac arrhythmias and sudden death";[7] "The application of nonlinear systems theory to electrophysiology ... may have clinical implications."[7] In a recent paper, describing a relation between T wave alternans in dogs with acute coronary artery occlusion and subsequent fibrillation, it was claimed that "a new approach is provided for quantification of susceptibility to malignant arrhythmia" and that "T wave alternans may represent a prechaotic state because bifurcate behaviour is the hallmark of chaos."[11]

These quotes indicate that a great deal is expected from studies applying chaos theory to cardiac rhythms: more insight into arrhythmogenic mechanisms and the identification of individuals at high risk for sudden cardiac death. It is here that I have my doubts. Certainly, new avenues should be explored, and possibly "we are sure to see dramatic advances in the field"[12] if we use nonlinear dynamics as a tool to study complex cardiac rhythms. In my view, however, cardiac arrhythmias ultimately have to be understood in terms of cardiac electrophysiology, and are due to changes in variables such as conduction velocity, excitability, automaticity, afterdepolarisations, electrotonic interactions between areas in the heart with different electrical properties, which in their turn are due to changes in properties of ionic channels, pumps, and receptors in cellular and subcellular membranes. Is my understanding that T wave alternans may be a harbinger of ventricular fibrillation in acute ischaemia improved because it is a prechaotic state (presumably leading to "chaotic" fibrillation where chaos is used in the old sense and not in the modern one) or because it marks the development of post-repolarisation refractoriness which sets the stage for unidirectional block, one of the prerequisites for re-entry?[13 14]

In my opinion our insight into arrhythmogenesis will be advanced by the application of chaos theory only if the link between "modern" chaos theory and "old fashioned" electrophysiology is established. Here, a mathematician who can model iterative non-linear systems and who understands the language of the cardiac electrophysiologist and of the practicing cardiologist may be of help.

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1 Young DA. Payment policy, quality of care and decision making with inadequate information. *J Am Coll Cardiol* 1989;14(suppl A):3A–6A.
2 *Dorland's illustrated medical dictionary.* 25th ed. Philadelphia, London, Toronto: WB Saunders, 1979.
3 *Webster's third international dictionary.* Springfield, Illinois, MA: G and C Merriam, 1971.
4 Li TY, Yorke JA. Period three implies chaos. *Am Math Monthly* 1975; 82:985–92,
5 Glass L, Mackey MC. *From clocks to chaos. The rhythms of life.* Lawrenceville NJ: Princeton University Press, 1988.
6 Chialvo DR, Michaels D, Jalife J. Supernormal excitability as a mechanism of chaotic dynamics of activation in cardiac Purkinje fibres. *Circ Res* 1990;66:525–45.
7 Vinet A, Chialvo DR, Jalife J. Irregular dynamics of excitation in biologic and mathematical models of cardiac cells. *Ann NY Acad Sci* 1990; 601:281–98.
8 Pyeritz RE, Murphy EA. Genetics and congenital heart disease: perspectives and prospects. *J Am Coll Cardiol* 1989;13:1458–68.
9 Goldberger AL, Bhargava V, West BJ, Mandell AJ. Some observations on the question: Is ventricular fibrillation chaos? *Physica D* 1986;19:282–9.
10 Kaplan DT, Cohen RJ. Is fibrillation chaos? *Circ Res* 1990;67:886–92.
11 Nearing BD, Huang AH, Verrier RL. Dynamic tracking of cardiac vulnerability by complex demodulation of the T wave. *Science* 1991; 252:437–40.
12 Glass L. Is cardiac chaos normal or abnormal? *J Cardiovasc Electrophysiol* 1990;1:481–2.
13 Downar E, Janse MJ, Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. *Circulation* 1977;56:217–24.
14 Janse MJ, Wit AL. Electrophysiological mechanism of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989;69:1049–69.

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REFERENCES: 1. White WB, Dey HM and Schulman P. Am Heart J 1989; **118:** 782-795. **2.** Kannel WB. Am J Med 1983; **75:** 4-11.

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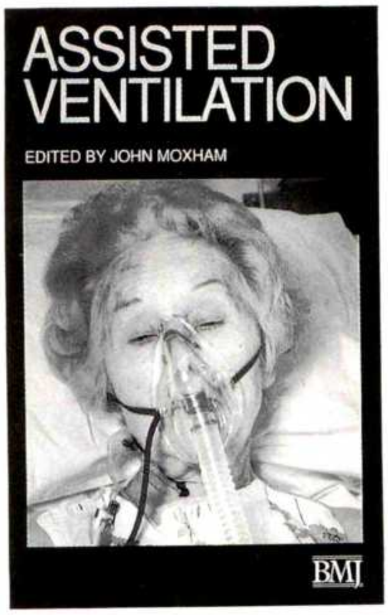

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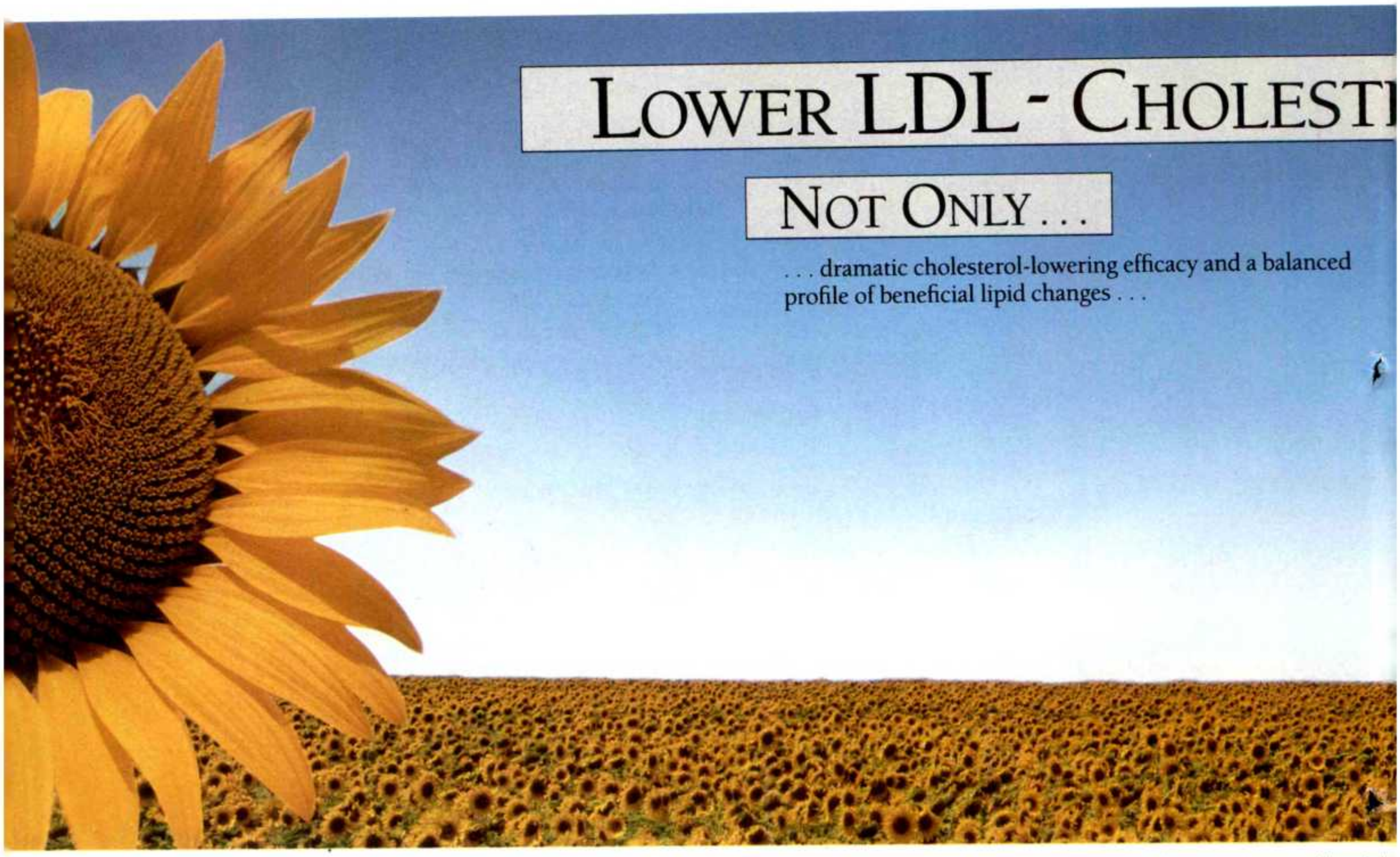
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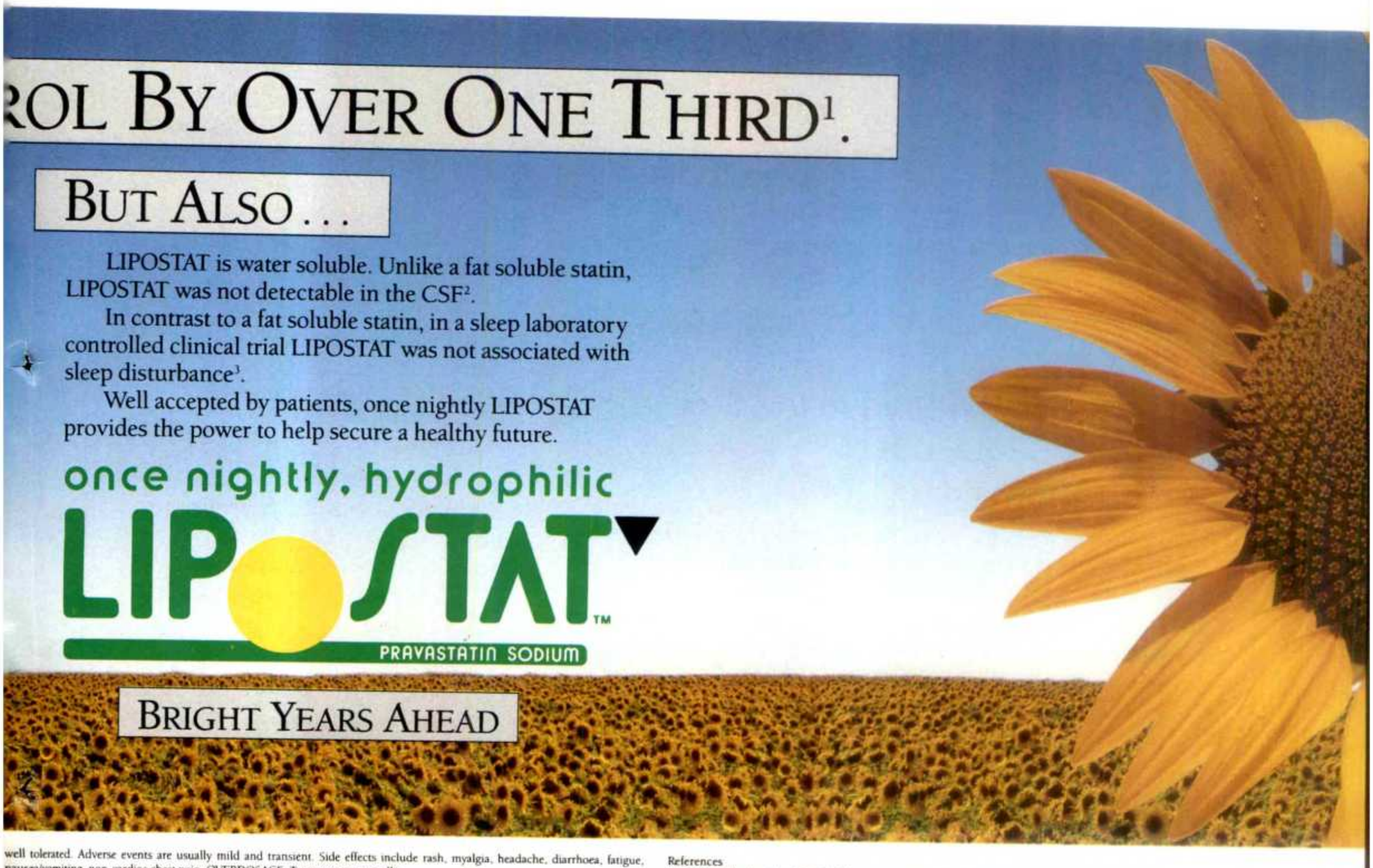

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References
1. Data on file. In trials LIPOSTAT demonstrates an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).
2. Botti RE et al. Clin Neuropharm 1991, **14 (3)**: 256-261.
3. Bixler EO. Round Table Discussion, Lipid Management, Pravastatin and the Differential Pharmacology of HMG-CoA Reductase Inhibitors. Proceedings of a panel discussion held in London on 5th July 1989. Royal Society of Medicine Services Round Table Series 1990, 16:

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BRITISH HEART JOURNAL

Dr Dennis M Krikler: Editor of the *British Heart Journal* 1981–91

Dennis Krikler has been editor of the *British Heart Journal* for eleven years. During his tenure the journal has become a medium for the publication of high quality research papers in clinical cardiology. The scientific merit of the papers is matched by the quality of the editorial presentation and accuracy of the references, both always major concerns of Dennis Krikler. The citation index of the *British Heart Journal* is very respectable for its size, and at a more mundane level an astute business sense has helped Dennis Krikler to make handsome profits for both the British Cardiac Society and the British Medical Association who are joint partners in the publication. Scientific journal publishing is changing and journals must respond to the needs and desires of their readers. Part of this change has been the need for more reviews and postgraduate education in cardiological science in the broadest sense. Dennis Krikler has foreseen this change and strengthened these aspects of the journal. In this regard his close links with the American College of Cardiology and its extended learning programme (ACCEL) gave him wide access to current thinking in both basic science and clinical practice and led to many reviews appearing in the *British Heart Journal*. Dennis Krikler has always had an innate ability to detect the new approaches and facts that are important in altering concepts in management and treatment.

Dennis Krikler has a style of editorship that avoids many of the pitfalls inherent in the position—so admirably outlined by Stephen Lock in this issue. Part of the style is the close interest taken in every paper. His letters to reviewers show clearly he has read the article; reviewers are selected personally, not as a random computer generated name. His letters to reviewers identify the strengths and weaknesses of the paper, as he sees them, without any hint of a closed mind on the subject. Questions are asked of the reviewers. These are attributes of the journal that we who follow him will need to continue.

All of these facets of Dennis Krikler combine to ensure a high quality scientific journal. The new editors and the editorial committee have a hard act to follow but they have a firm bedrock on which they can and must build.

The contents of this first issue of 1992 are a tribute to the editorship of Dennis Krikler. Many of the papers and reviews have an electrophysiological flavour reflecting the deep interest and advances he has made in this field.

There are personal appreciations giving a clear account of Dennis Krikler's wide international reputation as a clinician, scientist, and editor. His friends truly span the globe. Dennis Krikler's own contributions to this issue cover, at one extreme, an analysis of torsades de pointes while, at the other, his knowledge of the literature led to studies on the histogenesis of atrial myxomas. It is particularly appropriate that the issue contains an important report confirming the gene defect in the family from which Donald Teare described one of the first cases of hypertrophic cardiomyopathy. The disease is one in which Dennis Krikler has always had a deep interest and has himself published on the drug treatment. The original paper by Teare in 1958 has been a "best seller" in the

British Heart Journal and the subject of a *Current Contents* citation classic review. It is an interesting reflection on the progress and history of medicine that within 34 years an important cardiac condition was taken from a first morphological description through increasing clinical recognition and finally to the definition of its molecular basis. Dennis Krikler has always had a deep interest in the history of cardiology and his lectures on this topic are truly scholarly and have been given to many national and international societies. It is also particularly seemly that the issue is rounded off by the Fourth Report of a Joint Cardiology Committee spotlighting the current state of British cardiology.

M J DAVIES
Editor, *British Heart Journal*

Dennis Krikler: the editor

When I was president of an international association of science editors I amused myself by pigeon-holing the editors of medical specialty journals into at least four groups. The first, *Editor potestativus* had that brand of arrogance characteristic alas of many doctors. Their knowledge and skills far outshone those of any expert, given that they knew more about architecture than the architects, high finance than full-timers in the City, and law than QCs. As new editors they were similarly quick to perceive the iniquities of publication practices: for them, peer reviewers could and would provide better reports, more quickly; in future, there would be none of these senseless delays of five or six months in publishing, for under their guidance printers would reduce these to two months, or even less; and a word with the publisher's promotion department would ensure that the journal quadrupled its circulation to the 10 000 that only managerial incompetence had prevented its attaining. The learning curve of these editors and the obvious eventual outcome took up a lot of everybody's time; more importantly these dissipated the editor's energy and his creativity (the protagonist was almost always a he, for women doctors have much more humility). But the result was that during this editor's reign the journal stood still.

Any evolution of the journal was similarly hindered by my second type of editor, *Editor negativus*, or the abominable no man. Why should his journal change at all? New formats or features might be all right for the *British Journal of Omphalology*, but were not right for his journal. No further expert was needed to carry out that newfangled concept of statistical review, for if it were needed (and it very rarely was), why he and his fellow reviewers were quite skilled enough. And as for that proposal of structured abstracts, no he had not had the time to read the arguments in favour, but it was only yet another proposal by that self appointed bunch of full-time globe trotting editors—and he knew that the resulting illiterate mishmash would appeal to no one.

Thirdly, there was the *Editor planus* ("my brother is an hairy man, but I am a smooth man"). Appointed by his society, he was concerned solely to remain in its good books, with the prospect of ultimate preferment to its presidency. As a result, the journal was dominated by society affairs: papers were judged on who had written them, and not on merit, and expensive pages of an international journal were occupied by trivia better suited to a parish magazine. Readers and authors were quick to realise what had happened and went elsewhere; more sadly, perhaps, to right these wrongs they started yet another journal.

Here I have to break off lest somebody assume that all this is based on a 17 year experience as chief executive of the *BMJ*. It is not. To be sure, it would be unconvincing to claim that none of our specialist journals had ever had a Mr Potestativus, a Dr Nihil, or a Professor Smoothie as its editor; the statistics of chance alone would ensure that they had. The surprising feature, however, is that they could be counted on the fingers of one hand, and the calibre, energy, and contribution of the remainder were outstanding. For there is a fourth type of editor, the *Editor perfectus*—usually typified by an outstanding clinician turned humble and creative editor—and none is a better example than Dennis Krikler.

Given his achievements in cardiology (described elsewhere in this Festschrift), where has Dennis found the time to develop the *British Heart Journal*? For develop it he has. Not for him the thalamic technique of editing devised by some who want the kudos without the work—sending each article to two referees, taking their advice if they agree on acceptance or rejection or soliciting a third view if they disagree. Most referees have had personal letters from Dennis (who has already read the article in detail), and so have the authors eventually—to the dismay of the accountants but to the delight of the recipients and the betterment of the specialty. He has developed a strong back-up system: an editorial committee covering the subspecialities of cardiology as well as an inner cabinet of assistant editors. Nor has he neglected to ensure the editorial succession, identifying early somebody both able and willing to do the job and giving him suitable experience.

As a result under Dennis the *British Heart Journal* has stood out from the general run of specialist journals for several reasons. Firstly, it has vigorously supported peer review for ensuring the high quality of the original articles, a policy that also included the early recognition of the frequent need for formal statistical review as well. Secondly, it has taken on the major journalological issues: the value of structured abstracts, the wastefulness of duplicate publication, and the need for vigilance in detecting fraudulent results. Thirdly, it has retained the civilised feel set by Dennis's predecessors, particularly Walter Somerville and Kenneth Shirley Smith: the journal still prefers a literary style, abhorring abbreviations and jargon, and ensuring that the artwork is of the highest standard (particularly the quality of the colour reproduction).

Despite all the evidence to the contrary, doctors persist in complaining about a "literature explosion" or an "unchecked proliferation" of medical journals. But scientists have written and published at much the same rate and for much the same reasons for centuries, and, quite legitimately, as disciplines evolve with further sub-specialisation ever more journals are needed to serve them. The corollary is, of course, that the major specialist journals have had to become increasingly the general journals of their discipline, taking on some of the attributes of the non-specialist journals such as the *Lancet* or the *BMJ*. Thus to the original aim of the specialist journal—recording information about new research findings—has been added the other attributes of the general journal: instruction (editorials and review articles), unsolicited comment (letters to the editor), and miscellaneous (book reviews, news, points of view, and so on). When the new design of the *BMJ* specialist journals was introduced Dennis Krikler showed the mixture of conservatism and radicalism that I suspect is the ideal recipe for an editor of any specialist journal. On the one hand, he fought hard to retain the visual identity of the journal, settling for the compromise of the white cover with a peripheral maroon band. On the other hand, he followed his own inclination, seizing the opportunity to expand some existing features in the journal and to introduce several new ones—including book reviews and particularly the historical vignettes (for, as his curriculum vitae shows, he has a longstanding interest in the history of cardiology, particularly electrocardiology).

Dennis's many friends at the *BMJ* will miss the unusual combination of competence, breezy energy, and emollient charm. But when the history of the specialty in Britain comes to be written, the signal importance of his editorial role at a crucial time will be recognised; *si monumentum requiris, circumspice*.

STEPHEN LOCK
Editor, *BMJ*, 1975–91

BRITISH
HEART
JOURNAL

Achievements in the United Kingdom

It is a pleasure and privilege to contribute to this Festchrift for Dennis Krikler on his retirement as editor of the *British Heart Journal.*

Dennis arrived in the United Kingdom in 1967 with a high reputation from southern Africa, his last post there being consultant physician to the Salisbury Area Hospitals in what was then Rhodesia. He was appointed consultant physician to the Prince of Wales General Hospital and St Anne's Hospital in north London. He quickly set about consolidating his teaching activities, and rapidly made a name for himself with his electrocardiographic teaching sessions, and in 1969 he became clinical tutor to the North London Postgraduate Medical Centre.

Dennis soon became well known in cardiological circles in the United Kingdom, especially in London where he contributed to many meetings, and I well remember an excellent paper of his at a meeting of the Junior Cardiac Club at the Brompton Hospital. His election to the British Cardiac Society was assured and he became a member in 1971.

I came into close association with him when he joined the consultant staff at the Royal Postgraduate Medical School at Hammersmith Hospital—a joint appointment with King Edward Memorial Hospital at Ealing. He was a delightful and most helpful colleague and I was fortunate to work with him on problems of arrhythmia in hypertrophic cardiomyopathy and on many clinical occasions. He has been involved in organising, and participating in, many cardiological courses at Hammersmith notably on cardiac arrhythmias. For one of these courses he proposed that the title should be "The Electric Heart". In my elderly reactionary way, I thought this was rather avant-garde even for Hammersmith! But his gentle tactful perseverance persuaded me that this was an interesting and stimulating title (as indeed it was and as the enthusiasm for the course showed).

Dennis is an excellent teacher; as a lecturer his message is clear, his illustrations superb, and his command of his audience always complete. His expertise in electrocardiography in general and in electrophysiology in particular has gained him recognition in Europe and around the world—as the high regard in which he is held by experts in the field, such as Puech, Fontaine, Surawicz, Myerberg, Fisch, and many others testifies. He was a great friend of the late Leo Schamroth.

A large part of Dennis's contribution to British cardiology is his understanding and knowledge of arrhythmias, and his promotion of scientific clinical electrocardiography as an important area of cardiological research was a notable landmark. At Hammersmith he set up his programme of electrophysiological testing, and those he trained are now leading experts. In 1973, he obtained the MD for his thesis on the Wolff-Parkinson-White and related syndromes.

His achievements while in the United Kingdom have been widely recognised at home by his election to the fellowships of the Royal College of Physicians of London and Edinburgh and around the world by the Sir William Osler Award of the University of Miami in 1981, the Paul Dudley White Citation for International Achievement of the American Heart Association, and the Medal of Honour of the European Society of Cardiology. He was elected an honorary fellow of the Council of Clinical Cardiology of the American Heart Association, and to the fellowship of the American College of Cardiology.

Dennis's professional talents are not confined to clinical cardiology and electrocardiography. In 1976, he became treasurer of the British Cardiac Society and proved remarkably effective in this role as I can testify as a former treasurer of the society. His skill at writing and editing was soon recognised by his appointment as assistant editor and finally editor of the *British Heart Journal.*

His clinical and teaching distinction, his research output, his frequent invitations to contribute to important scientific meetings overseas, and a successful private practice give him little time for extramural activities. Nevertheless, his interest in the theatre and opera remains keen. His distinction has been recognised by the Freedom of the Worshipful Society of Apothecaries in 1989, while in 1990 he was made a Freeman of the City of London. He has held no fewer than 21 visiting professorships and named lectureships worldwide from 1979 to 1990.

The dry bones of even the most distinguished biography do not necessarily do justice to the individual. Dennis's quiet, friendly bearing and cheerful mien are reassuring to all and much appreciated by his colleagues, patients, and students. He never patronises, never attempts to diminish the qualities of his associates, and often illustrates a discussion with gentle irony and occasionally with flashes of mischievous (but never malicious) humour. His obvious distinction makes his modest approach all the more impressive.

Dennis is always willing to help, and Walter Somerville once told me that apart from his editorial skills and literary powers, Dennis's great attribute as an assistant editor was his willingness to take on any responsibility or chore without hesitation. His gift for languages is an asset in his editorial role and in his work with European colleagues.

Dennis's contribution to the *British Heart Journal* and his achievements in the United Kingdom will always earn him the greatest regard and respect.

JOHN GOODWIN
Emeritus Professor of Clinical Cardiology, Royal Postgraduate Medical School.
President, British Cardiac Society 1972–1977

An American tribute

As Editor of the *Journal of the American College of Cardiology (JACC)* I deem it a great privilege to join the Festschrift dedicated to Dennis Krikler who retires as editor of the *British Heart Journal.* Dennis has capped his career by his outstanding record as editor of the journal. During his tenure the journal has maintained its high reputation for scientific content, scholarship, and readability. It continues to publish outstanding papers from major cardiovascular centres not only in the United Kingdom but also in Europe and the United States. In fact, American authors consider it a great achievement to have their papers published in the *British Heart Journal.*

I have had a very close personal relationship with Dennis which dates back to the days when he served as assistant editor of the journal under Walter Somerville. He would accompany Walter at the annual meetings of the American College of Cardiology and its editorial board. When Dennis succeeded Walter as editor 11 years ago I encouraged and urged him to continue to attend the annual meetings of our editorial board, which he did. He took active part in our discussions and exchange of ideas on mutual editorial policies and problems and we would look forward to his presentations and wise counsel based on his own experience.

At one meeting Dennis gave a stimulating slide presentation on how an author should prepare an article that would pass peer review and please the editor and be acceptable to both of our journals. All the members of the editorial board were taking notes to pass on to their staff! At another meeting he was enthusiastic about the new and elegant appearance of and format of the *British Heart Journal* which made it more attractive and readable. There were many favourable comments from the board.

Dennis has always been intensely interested in medical terminology in current use. When Walter Somerville was editor he was strongly in favour of stopping the term dysrhythmia which had become very fashionable. He was strongly in favour of retaining the term arrhythmias based on his analysis of the Latin derivation of the term. With Dennis we spent much time debating whether the term dilation was more appropriate than vasodilation and whether valvuloplasty was more accurate than valvulotomy for the procedure of balloon dilatation of the mitral or aortic valve. Both Dennis and I favoured the use of the terms aortic or mitral balloon dilatation. Valvulotomy and commissurotomy would be reserved for describing the surgical technique. Both Dennis and I felt that there should be more consistency among journal editors as to the use of these various terms.

After the 1989 meeting of the American College of Cardiology in Anaheim, California, Dennis continued his American tour and proceeded to San Francisco, just in time to see the effects of the earthquake. The account of his experiences that he sent to me was spellbinding.

The *British Heart Journal* turned 50 in January 1989. Its longstanding growth and success have been due to the efforts and dedication of editors such as Dennis Krikler. The editorial board of *JACC* and I enjoyed and learned a great deal from his wise counsel and the discussions we had together.

Mike Davies, the associate editor of the *British Heart Journal*, succeeds Dennis as editor in January 1992. He has already been introduced to the editorial board of *JACC* at its last meeting in March 1991. I am due to retire as editor of *JACC* in July 1992 but I hope that he will continue the longstanding tradition of attending the annual editorial board meetings of *JACC* and share his experiences and problems with the new editor of *JACC*. I look forward to seeing Dennis and Mike at the April 1992 American College of Cardiology meeting in Dallas, Texas. The outgoing and new editors of our journals will celebrate.

SIMON DACK
Editor, *Journal of the American College of Cardiology*

Member of the French Society of Cardiology

After 11 years as the editor of the *British Heart Journal*, Dennis Krikler has decided to retire and to leave his place to Professor Mike Davies. This is understandable. Dennis has assumed this important task with a presence, a constancy, and attentiveness without neglecting his academic obligations, his work as a consultant at the Hammersmith Hospital, his private practice, his trips abroad, and his intensive writing of articles and chapters. Thanks to this fantastic work, he has maintained the *British Heart Journal* among the top cardiological publications and there is no doubt that British cardiology owes him a lot.

I could make these few lines into a classical panegyric. I could remind you that he is a member of all the great societies of cardiology in the world, that he has received numerous plaudits for his work (I will just mention the Sir William Osler Award, Miami 1981; the Paul Dudley White Citation for International Achievement which he received at the American Heart Association meeting in 1984; the medal of honour which the European Society of Cardiology awarded him in 1990). I could name his numerous publications on arrhythmias, the lectures he gave all over the world, his contributions to books that every cardiologist should have in his or her library.

However, I would rather take the opportunity the *British Heart Journal* is offering me to recall more personal souvenirs. When we had our first contact more than 20 years ago I knew Dennis Krikler only by name and reputation. He was calling from London and we had a violent argument about a bibliography problem; based on the tone of his voice, I imagined a man much younger than myself on the other end of the line. I was wrong. When we met soon after, I discovered that he was much older than I (10 December 1928 versus 16 July 1929). And that is how a faithful friendship was born.

Since then I have met Dennis on many occasions in London, in Paris, in Marseilles, in Chicago, in Atlanta, in San Francisco, in Washington or elsewhere in the world during congresses and symposiums. I always admired the quality of his lectures and I can say that I have seldom met such a combination of scientific value and good clinical commonsense. He knows better than anyone not only modern cardiology but also the history of cardiology. It is always an extraordinary pleasure for me to see him comment on slides reproducing ECG recordings from 1913, pictures of such-and-such a pioneer cardiologist, or parts of books several centuries old. And lastly, of particular value for poor French cardiologists condemned to attempt to speak in English at international congresses, his diction is irreproachable, clear, aesthetic, well articulated, creating in French listeners the delusion that their knowledge of English has improved remarkably . . . till the next speaker arrives, Texan or Irish, dragging you back into depression.

Dennis Krikler is one of the foreign cardiologists the French Society of Cardiology is proud to count among its Members of Honour. I think he is one of the French Society's best friends and that he likes our country, its good food and luxury hotels, for this scientist is also a sybarite. He appreciates and knows our good wines very well as I discovered on the fiftieth anniversary of our society, on a beautiful spring night in Paris in May 1987. He speaks our

language very well, with a delicious accent, and expresses himself very elegantly in French when he stays in our country.

I am sure that Mike Davies, who is succeeding Dennis as editor of the *British Heart Journal*, will keep the journal at its present high level. I know that our two societies, through their meetings and their journals, will maintain more than ever their cooperation and friendly relations. But above all, I am quite sure that for a long time, when someone speaks about British cardiology and the *British Heart Journal*, all over the world and especially in France, one name will immediately come to mind—that of Dennis Krikler.

ROBERT SLAMA
President, *French Society of Cardiology*

Approches methodologiques et therapeutiques en rythmologie

Le départ d'un ami, qui présida durant plusieurs années aux destinées d'un grand journal de cardiologie, est une bonne occasion de réflexion sur le chemin parcouru avec lui par ailleurs depuis de nombreuses années dans une discipline ayant notre intérêt commun. Notre génération ne prétend pas avoir inventé la rythmologie (tout au plus le vocable) après que de grands auteurs tels que Lewis au Royaume-Uni, Gallavardin en France, Langendorf aux USA, aient en fait décrit presque tous les concepts que nous utilisons. Mais nous avons eu la chance depuis un quart de siècle d'avoir pu exploiter le développement des techniques. Vers la fin des années soixante ce fut l'électrophysiologie invasive, avec la possibilité enfin donnée de manipuler les troubles rythmiques pour mieux les étudier. Dix ans plus tard, l'ère informatique transformait la philosophie même de la méthode de Holter, d'une simple technique d'observation en un outil performant de quantification et de compréhension. Pour avoir avec Dennis Krikler vécu les enthousiasmes de la collection de cas exceptionnels,[1,2] puis avoir à son instigation mis en garde dans ce journal-même contre les inconvénients d'une approche trop purement technique des problèmes rythmologiques,[3] nous souhaitons lui dédier quelques réflexions sur l'évolution de notre discipline dans les dernières années.

TECHNIQUES D'EVALUATION ET SYMPTOMATOLOGIE CLINIQUE

Trop vite, on a voulu tirer des investigations des indications pronostiques trop péremptoires et indépendantes d'autres aspects de la cardiopathie en cause. Trop directement on a voulu voir dans la précision des évaluations quantitatives l'équivalent d'une rigueur dans l'évaluation des médicaments. Trop facilement on a pensé élargir au coeur entier et au patient le bénéfice apparent du contrôle des arythmies. Dans tous ces domaines des limites sont progressivement apparues. Les tendances défavorables d'abord observées étaient au gré des tempéraments expliquées par une certaine philosophie des troubles du rythme et de leur place dans la cardiopathie qu'il fallait donc repenser, ou par une rigeur méthodologique insuffisante qu'il fallait donc renforcer dans une sorte de fuite en avant.

Pourquoi traite-t-on les arythmies? S'agissant des symptômes la réponse est en principe assez simple mais il faut bien voir que ces symptômes vont de la simple palpitation liée à une extrasystole à la mort subite par fibrillation ventriculaire. Entre les deux se situent les arythmies si mal qualifiées de "menaçant la vie". Elles peuvent être "symptomatiques", avec l'euphémisme et l'imprécision que comporte ce terme d'ailleurs non équivalent dans toutes les langues. Finalement, la différence n'est pas dans le fait que la palpitation est un symptôme et la mort subite un tournant évolutif définitif de la mort subite: la différence est que l'extrasystole et la fibrillation ventriculaire, du simple point de vue rythmologique, ne reconnaissent pas les mêmes déterminants, donc pas le même traitement. Pire encore, on en vient à craindre que les médicaments efficaces sur les premières ne se révèlent nocifs sur les seconds, et réciproquement.

ARYTHMIES, FONCTION VENTRICULAIRE ET ISCHEMIE

Le résultat cohérent d'études de suivi des patients ont lié la notion de mort subite, ou plus simplement de mort cardiaque à la présence d'un plus grand nombre d'arythmies ventriculaires, à l'altération plus prononcée de la fonction ventriculaire, à l'évidence plus fréquente d'une ischémie, silencieuse ou non. En établissant des corrélations indiscutables avec l'évolution plus ou moins troublée, on n'a certes pas nommément désigné les coupables. Mais le moins que l'on puisse dire est que l'attention n'a guère été attirée sur la règle générale selon laquelle corrélation ne signifie pas relation de cause à effet. On a ainsi confondu marqueur du pronostic et facteur causal de la mort, et choisi comme cible thérapeutique ce qui n'est sans doute bien souvent qu'un témoin. Les traitements symptomatiques de l'ischémie, de l'insuffisance cardiaque, et des arythmies ont ainsi été utilisés sans succès. Non seulement ils n'apportent pas, au sein des grands essais conduits, la preuve statistique d'un bénéfice thérapeutique, mais on doit souvent charitablement passer sous silence les tendances inverses présentes dans le groupe traité par tel puissant antiangineux, tel agoniste bêta-adrénergique améliorant pourtant les performances physiques, tel antiarythmique éradicant sans pitié les extrasystoles ventriculaires.

Les bêta-bloquants

Comme chacun sait, seuls les bêta-bloquants ont jusqu'ici globalement apporté la preuve de leur efficacité dans l'amélioration de la survie des patients.[4] Pourtant classiquement contrindiqués dans l'insuffisance cardiaque, dépassés au titre d'anti-angineux par les vasodilatateurs et les antagonistes du calcium, guère prisés des rythmologues et ne formant guère que de nom une classe particulière d'antiarythmiques, les bêta-bloquants ont donc assez l'allure d'outsiders figurant à l'arrivée, dont on ne s'inquièterait guère de savoir comment et pourquoi ils y sont parvenus. Il est trop facile d'y voir une conséquence de l'action anti-ischémique quand on sait que leur effet favorable se manifeste dans les cardiomyopathies comme dans l'insuffisance coronarienne. Il est aussi un peu facile de penser que leur effet se manifeste malgré l'insuffisance cardiaque alors que ce sont précisément les groupes de patients ayant la fonction cardiaque la plus altérée qui bénéficient le mieux du traitement.[5] Enfin il est bien trop facile de dire qu'un effet antiarythmique éventuel n'est guère en cause à partir du moment où les standards requis pour le traitement des extrasystoles ne sont pas respectés. Et curieusement, la question de savoir si l'effet bénéfique des bêta-bloquants n'est pas tout simplement lié à leur effet antiadrénergique n'est guère évoquée.

Le grand responsable de la stimulation adrénergique est l'insuffisance cardiaque. Nous laissons volontiers à plus qualifés que nous le soin de montrer comment les bêta-bloquants sont sans doute les seuls médicaments capables de rompre le cercle vicieux établi entre les mécanismes de défense et leurs conséquences finalement pernicieuses. Le dogme de la contrindication du blocage bêta-adrénergique est en passe de disparaître, mais on est encore loin de savoir dans quels cas ce blocage a le plus de chances d'être utile et toléré, si tous les produits actifs sont également efficaces, et à quelle dose ils le sont. Les effets bénéfiques, également prouvés, des vasodilatateurs et notamment des inhibiteurs de l'enzyme de conversion de l'angiotensine, amènent à penser qu'en fait les bêta-bloquants n'excercent une action favorable que malgré un effet symptomatique qui ne l'est pas, alors qu'on s'accommoderait mieux d'un traitement soulageant les symptômes tout en abordant au fond le problème et en réduisant la stimulation adrénergique délétère.

Les anti-arythmiques

Dans la relation arythmies-anti-arythmiques, il y a un problème de fond à régler. En quelque sorte une crise latente de longue date ne peut plus être ignorée depuis la publication des résultats de l'étude CAST.[6] Le grand mérite, d'ailleurs possiblement le seul, de cette étude est d'avoir rendu incontournable un problème régulièrement écarté. Il est maintenant démontré qu'utiliser des antiarythmiques purs pour supprimer des arythmies asymptomatiques aggrave la mortalité. Le fait était suggéré par des études analogues, qui ne devaient leurs conclusions incertaines qu'à l'efficacité moindre du médicament choisi, à la vérification moins attentive de cette efficacité, au nombre moindre des patients inclus. Pour n'en citer qu'une, rappelons les chiffres de mortalité de l'étude IMPACT[7] curieusement identiques (7,6%) à ceux du CAST (7,7%), il est vrai après un an de suivi au lieu de 10 mois, et sur un total de 630 patients au lieu de 1455. Cette dernière différence suffit à rendre significative ce qui n'était qu'une tendance. La différence de mortalité entre les groupes placebo (4,8% dans IMPACT, 3% dans CAST) vient aggraver l'évidence en soulignant la mortalité de la phase d'inclusion du CAST durant laquelle tous les patients étaient traités.

Outre que la faisabilité de futurs essais de prévention de mort subite est maintenant bien compromise, le plus gênant est que force est de constater qu'en fait rien n'est réglé.[8] Pour des raisons éthiques, on ne pourra plus accepter de protocole impliquant un risque significatif pour un groupe traité par les antiarythmiques, mais pourtant CAST pas plus qu'IMPACT ne permet de réfuter l'hypothèse que certains patients relèvent bien du traitement antiarythmique. La situation est la même pour les bêta-bloquants, avec des raisons opposées: la faisabilité de nouvelles études est compromise par la crainte de priver le groupe placebo du bénéfice démontré du traitement actif. Il n'est pourtant pas discutable que tous les groupes ne bénéficient pas du traitement, que certains patients meurent subitement sous bêta-bloquants, mais lesquels? En somme, le fait est que, dans un cas comme dans l'autre, on ne s'est pas donné les moyens de comprendre, fût-ce a posteriori. Ainsi nombre d'études incluant les bêta-bloquants n'ont pas comporté d'enregistrements Holter.[4] Quant aux études incluant les antiarythmiques, elles n'ont pas posé au Holter les bonnes questions, ne s'attachant qu'à une quantification pure et dure des arythmies observées, non à leur environnement, aux déterminants de leur survenue.

ARYTHMIES SYMPTOMATIQUES ET ARYTHMIES LETALES

On a trop tendance à oublier que les classifications actuelles des arythmies en termes de simples ou de complexes, ou encore "menaçant la vie", ne font que couvrir de grandes insuffisances de connaissance. Sans jouer sur les mots, on peut dire qu'une caractéristique importante d'une arythmie "menaçant la vie" est d'abord de ne pas l'avoir ôtée jusque-là au patient. Le terme se rapporte à un risque statistique, non à un mécanisme électro-physiologique. La présence d'arythmies ventriculaires répétitives, plus ou moins polymorphes, est menaçante par l'indication qu'elle donne sur la survenue possible d'arythmies létales. Mais si l'élément déterminant de celles-ci est la stimulation adrénergique du substrat électrophysiologique, sa prévention est plus importante que le traitement plus ou moins cosmétique de son expression électrocardiographique a minima. Le vrai problème est de comprendre pourquoi et comment l'on passe d'une arythmie menaçant la vie à une arythmie létale. L'expérience acquise par l'analyse des cas de mort subite enregistrée montre bien leurs traits communs:[9] l'ischémie aigüe est plutôt rare avant les tachyarythmies, alors que l'évidence du facteur adrénergique est souvent attestée par l'accélération de la fréquence sinusale préalable au déclenchement. Mais ce témoin de stimulation adrénergique n'est pourtant pas plus constant, ou évident, dans ces circonstances extrêmes qu'il n'est constant, ou apparent avant les tachycardies ventriculaires non mortelles, celles qui ne vont pas dégénérer en fibrillation ventriculaire. Dans cette circonstance aussi nous avons montré[10] que le traitement bêta-bloquant est efficace, et augmente la longévité tout en manifestant son effet antiarythmique. Or l'absence ou la discrétion de l'accélération sinusale avant les arythmies ne peut être tenu pour un argument démontrant l'absence du facteur adrénergique. Peut-être même est-ce le contraire, tant il est vrai que la surcharge adrénergique elle-même tend à masquer ses propres critères, notamment par la diminution de la variabilité de fréquence sur laquelle on insiste actuellement comme un marqueur pronostique très fiable.

SYSTEME NEURO-VEGETATIF ET PARADOXES

Les rapports entre système nerveux végétatif et arythmies ventriculaires sévères sont truffés de paradoxes. Paradoxe d'une fréquence cardiaque dont les possibilités d'adaptation, notamment d'accélération franche sont diminuées, et d'autant plus que l'insuffisance cardiaque s'aggrave et comporte une stimulation adrénergique plus forte. Paradoxe d'arythmies adrénergiques dont le marqueur est peu visible peut-être justment à cause d'une sensibilité accrue à ce facteur adrénergique.[11] La tachycardie ventriculaire survenant à l'acmé d'une épreuve d'effort maximale n'est probablement pas, et de loin, celle qui relève le plus du traitement bêta-bloquant. L'origine adrénergique ne fait pas de doute, certes, mais le substrat n'est sans doute pas très susceptible puisqu'une stimulation forte lui est nécessaire. Paradoxe enfin que la réduction de la mortalité plus grande dans les groupes ayant une insuffisance cardiaque plus sévère, avec un effet antiarythmique plus patent des bêta-bloquants. Il existe une corrélation entre la réduction de la fréquence sinusale et le bénéfice en termes de réduction de mortalité.[12] Interprêter cette corrélation comme une relation de cause à effet est une faute de raisonnement analogue à celle qui conduit à traiter les arythmies asymptomatiques pour la seule raison qu'elles existent. Simplement, la fréquence sinusale des patients sous influence adrénergique est plus sensible aux bêta-bloquants, et il se trouve que ce sont eux qui bénéficient le plus du traitement. Il n'y aurait sans doute guère à espérer d'une réduction de fréquence cardiaque par un autre moyen que le traitement bêta-bloquant, et à ce jour aucun protocole ne se propose de tester cette hypothèse en faisant par exemple appel à la création artificielle d'une bradycardie par ablation du faisceau de His ...

Un dernier problème, peut-être un dernier paradoxe s'inscrit dans la ligne des précédents: celui de la posologie nécessaire à l'efficacité antiarythmique des bêta-bloquants. D'autres que nous dans la littérature utilisent ces médicaments pour traiter les arythmies ventriculaires. Certains utilisent des posologies normales mais réservent les indications aux patients sans insuffisance cardiaque. Ils concluent alors, à notre sens d'une manière non justifiée puisqu'ils limitent volontairement leur expérience, à un effet d'autant meilleur que la fraction d'éjection est plus élevée.[13] A l'inverse, dans le cas d'une altération profonde de la fonction myocardique et pour obtenir une meilleure tolérance, d'autres utilisent des posologies faibles de bêta-bloquants réputés moins puissants, avec la protection supposée d'un effet agoniste partiel. Et le fait est qu'une telle pratique est efficace, tant il est vrai que l'effet du médicament dépend plus du patient qui le reçoit que de sa puissance propre ou de sa posologie.[14] Quant à nous, dans le cadre des arythmies graves de l'insuffisance cardiaque, nous avons pour habitude d'utiliser progressivement des posologies normales, voire fortes, de bêta-bloquants puissants. Dans notre expérience la tolérance n'en est pas souvent influencée, à condition de s'affranchir de l'habitude maintenant prise de l'utilisation quasi systématique des inhibiteurs de l'enzyme de conversion de l'angiotensine. Son intérêt dans le traitement de l'insuffisance cardiaque ne fait pas de doute, mais son rôle dans l'amélioration de la mortalité passe peut-être par les mêmes voies que le traitement bêta-bloquant, et la mauvaise tolérance à celui-ci par les insuffisants cardiaques est dans notre expérience très généralement le fait d'une prescription combinée des deux types de médicaments: comme dans d'autres domaines il faut faire des choix, la pression artérielle de ces patients ne pouvant résister indéfiniment à la puissance des agents pharmacologiques.

LA DONNEE NOUVELLE DE LA DEFIBRILLATION AUTOMATIQUE IMPLANTEE

Le "primum non nocere" des anciens est plus que jamais d'actualité, et de fait la notion de sécurité doit primer sur l'efficacité. Sécurité du patient, mais efficacité sur le symptôme, plus important s'il est clinique que s'il est purement électrocardiographique. Lorsque les problèmes se rejoignent au niveau le plus élevé de la prévention de la fibrillation ventriculaire ou du risque de son déclenchement par les médicaments on est bien en peine de formuler des recommandations. La technique nouvelle de la défibrillation implantée vient peut-être à point nommé offrir une voie de sortie à cette véritable impasse. C'est le moment de se rappeler qu'en son temps l'introduction de la technique de la défibrillation externe fut à l'origine du développement de toute l'électrophysiologie invasive: celle-ci ne put en effet exister que lorsque fut levé le risque permanent de déclencher des catastrophes rythmiques par l'utilisation inconsidérée de la stimulation programmée.

Cette expérience est sans doute en passe de se renouveler à partir de la défibrillation implantable, à condition que nous sachions en saisir convenablement l'opportunité. En clair, cela signifie que tous nos efforts doivent être dirigés vers l'utilisation compréhensive de cette technique. Idéalement on imagine des essais randomisés sous le couvert de la protection du défibrillateur implantable. Mais il y a des obstacles: financier bien sûr, mais aussi éthique qui consisterait à implanter des patients dans le but au moins présent sinon exclusif de les traiter médicalement en incluant cette notion récente que l'on ne sait plus très bien lequel, du produit actif ou du placébo, est le mieux susceptible de garantir la vie du patient. Il serait choquant de commettre pour l'évaluation de la valeur réelle de cette technique des erreurs analogues à celles que la recherche d'une trop grande rigueur peut faire commettre dans l'évaluation des médicaments, en particulier appliquer sans discernement les purs principes du caractère prospectif et randomisé des études. Il y a sans doute d'autres voies, dont l'ambition doit être une meilleure compréhension. Quelle que soit la technique de traitement, évaluer globalement, statistiquement, ses mérites est finalement sans grand intérêt si l'on ne sait pourquoi le résultat est finalement bénéfique ou délétère. S'agissant de défibrillation implantée, la question n'est pas tellement de savoir combien de patients peuvent bénéficier de ce progrès, mais lesquels et pourquoi, afin de mieux en cerner les indications. Le parallèlisme est frappant entre l'électrophysiologie invasive, méthode provocative qui n'a existé que par la défibrillation externe, et la méthode de Holter, passive mais fructueuse puisque l'on est finalement ramené à des tentatives de compréhension des phénomènes spontanés. D'ores et déjà les renseignements disponibles à partir des défibrillateurs implantés ne sont pas aussi inexistants que dans le cadre de la stimulation implantée. Ils sont loin d'être suffisants cependant, et le développement du "Holter implanté" est bien aussi important pour l'avenir que celui de la défibrillation elle-même. Les obstacles techniques sont encore importants. Ils devront être surmontés, et ils le seront d'autant mieux que la demande en sera plus pressante de la part des utilisateurs que sont les cardiologues.

CONCLUSION

En rythmologie comme ailleurs, il n'est pas bon que l'outil utilisé conditionne la problèmatique. L'électrophysiologie invasive est considérée comme un mode d'investigation compréhensive: stimuler le coeur revient à poser une question au substrat, et à observer la réponse. La technique

de Holter nous met d'emblée en présence de la réponse qu'est l'arythmie, de sorte qu'on en oublie de poser la question, qui est de déterminer comment l'arythmie est survenue, quels sont ses rapports avec l'environnement en termes de fréquence, de charge adrénergique, mais aussi bien d'ischémie, d'insuffisance cardiaque, de troubles métaboliques. Là se trouvent les causes réelles, qui échappent aux approches de type épidémiologique dont les vertus sont ailleurs et les déductions thérapeutiques moins directes. On a vu qu'elles peuvent être sanctionnées de manière brutale, ce qui doit être l'occasion d'une révision déchirante d'hypothèses aventureuses et de méthodologies plus simplistes en réalité que rigoureuses.

Pour n'avoir pas suffisamment réfléchi au bien-fondé de leurs méthodes d'évaluation et de leurs attitudes thérapeutiques, les rythmologues doivent une fois de plus perfectionner les techniques pour valider les thérapeutiques. Pour l'instant ils sont en quelque sorte, parmi les cardiologues, sur la sellette. Mais une telle démarche pourrait certainement s'appliquer à bien d'autres domaines de la cardiologie.

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1 Krikler D, Curry P, Attuel P, Coumel P. 'Incessant' tachycardias in Wolff-Parkinson-White syndrome. I: Initiation without antecedent extrasystoles or PR lengthening, with reference to reciprocation after shortening of cycle length. *Br Heart J* 1976;38:885–96.
2 Coumel P, Attuel P, Slama R, Curry P, Krikler D. 'Incessant' tachycardias in Wolff-Parkinson-White syndrome. II: Role of atypical cycle length dependency and nodal-His escape beats in initiating reciprocating tachycardias. *Br Heart J* 1976;38:897–905.
3 Coumel P. Ambulatory electrocardiographic monitoring and the management of arrhythmias. Precision versus inflexibility. *Br Heart J* 1983;49:201–4.
4 The Beta-Blocker Pooling Project Research Group. The beta blocker pooling project (BBPP): subgroup findings from randomized trials in post-infarction patients. *Eur Heart J* 1988;9:8–16.
5 Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503–10.
6 The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.
7 IMPACT Research Group. International mexiletine and placebo anti-arrhythmic coronary trial. I. Report on arrhythmias and other findings. *J Am Coll Cardiol* 1984;4:1148–58.
8 Akhtar M, Breithardt G, Camm AJ, Coumel P, Janse MJ, Lazzara R, *et al.* CAST and beyond: implications of the Cardiac Arrhythmia Suppression Trial. *Circulation* 1990;81:1123–7 and *Eur Heart J* 1990;11:194–9.
9 Leclercq JF, Maison-Blanche P, Cauchemez B, Coumel P. Respective role of sympathetic tone and of cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holter monitoring. *Eur Heart J* 1988;9:1276–83.
10 Hermida JS, Coumel P, Leclercq JF, Cauchemez B, Maison-Blanche P, Leenhardt A, *et al.* Intérêt des bêta-bloquants dans le traitement des tachycardies ventriculaires récidivantes chez l'insuffisant cardiaque. *Arch Mal Coeur* 1987;80:290–300.
11 Coumel P. The management of clinical arrhythmias. An overview on invasive versus non-invasive electrophysiology. *Eur Heart J* 1987;8:92–9.
12 Kjekshus J. Heart rate reduction—a mechanism of benefit? *Eur Heart J* 1987;8L:115–22.
13 Brodsky MA, Byron JA, Luckett CR, Capparelli EV, Wolff LJ, Henry WL. Antiarrhythmic efficacy of solitary beta-adrenergic blockade for patients with sustained ventricular tachyarrhythmias. *Am Heart J* 1989;118:272–80.
14 Coumel P, Hermida JS, Leenhardt A, Maison-Blanche P, Cauchemez B, Leclercq JF, *et al.* Heart rate variability in myocardial hypertrophy and heart failure, and the effects of beta-blocking therapy. A non-spectral analysis of heart rate oscillations. *Eur Heart J* 1991;12:412–22.

Continental connections

Dr Dennis Krikler has retired as editor of the *British Heart Journal*. When I was asked to contribute to his Festschrift the title of the contribution was assigned to me and that did not make my task any easier.

Dr Krikler has and always has had many important connections on the continent. I assume that the continent of Europe is meant here. He has friends and admirers all over Europe; but not only in Europe, also in the United States, Israel, Australia, and Japan. He also has contacts in the Soviet Union and other eastern European countries.

I have known Dennis Krikler since the early 1970s. We worked together on a film on angina pectoris in which the beneficial role of calcium antagonists was stressed for the first time. Among our colleagues on the project were Dr Albert Fleckenstein, Dr Gisa Grün (later Mrs Fleckenstein), and Dr Winnifred Nayler. I learned so much in such a short time. With his well-chosen words, spoken in magnificent English, Dr Krikler dominated the discussions. We exchanged ideas on history, politics, current cardiology, and so forth. That is when our friendship began. I knew then that Dr Krikler was to be one of Europe's leading cardiologists.

Over the years I have come to know Dr Krikler as a warm human being, a truly reliable friend, an outstanding clinician, and a superb editor. Although he now steps down as editor of the *British Heart Journal*, Dr Krikler will remain active in international cardiology, appreciated by his overseas colleagues in Holland, the rest of Europe, and the United States.

Under the editorship of Dennis Krikler the *British Heart Journal* has flourished. Although the journal is British by heredity, form, and content, its impact extends well beyond the United Kingdom. The journal crosses the North Sea and the Atlantic Ocean, and finds its way to Japan, India, Australia, and South Africa.

The quality and popularity of the *British Heart Journal* today are attributable not only to Dr Krikler; his predecessors did a great job as well.[1] But with his scholarly approach, he has put a special stamp on the journal.

Not only the *British Heart Journal* benefits from Dr Krikler's editorial skills. Many readers may not know that Dr Krikler is co-editor of the tape journal of the American College of Cardiology.

Dr Krikler has a vast knowledge of modern and historical cardiology and a superb command of the Queen's English. It is always a pleasure to listen to his presentations. His text is lucid, his slides are magnificent, and he is very knowledgeable. He is a world renowned expert on the pharmacology of arrhythmias. Many readers of the *British Heart Journal* may not be aware that he, together with the late Dr Leo Schamroth, discovered the effect of verapamil on atrial fibrillation[2]—a breakthrough in the treatment of supraventricular arrhythmias. Dr Krikler is one of Britain's best cardiological ambassadors. Many cardiologists outside Britain regard Dr Krikler as the personification of the best of traditional British cardiology. He is a great teacher and the fact that he held appointments at postgraduate institutions meant that his undergraduate teaching has been limited. This is a pity because as one of my own teachers once remarked "students are the *raison d'être* of any university." Dr Krikler, of course, is involved in postgraduate teaching in London, but undergraduate students are the salt of the earth. In addition to the Best Editor Award he deserves the Best Teacher Award.

We all hope and wish that Dennis Krikler will continue as an oracle for young cardiologists and for his peers, for he is more than just a knowledgeable modern cardiologist. First and foremost Dr Krikler is a scholar—a rarity among modern cardiologists. He knows his classics and has an amazingly good and versatile memory. Just call him, and ask for this or that subject or author, and he will tell you.

It seems to me that Dennis Krikler's reputation in cardiology lies outside rather than inside Britain. If so, I do not know why. Is Krikler like a prophet not without honour, save in his own country? It seems that way, at least from the continental point of view. I do not know of anyone who has done more for present-day British cardiology than Dr Krikler. I for one would not know how to get along without him and international cardiology owes him a lot.

If I may finish with a personal word, my wife Annemarie and I wish him and his dear wife Anne, together with their children Shirley and Paul, many happy, healthy, and successful years. We hope that our friendship and contacts will flourish in the future as they have done in the past.

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1 Meijler FL. Walter Somerville. *Br Heart J* 1981;45:11–2.
2 Krikler D. Verpamil in cardiology. *Eur J Cardiol* 1974;2:3–10.

Japanese cardiology

For the past 20 years, Dennis (I hope Dr Krikler does not mind my calling him by his first name) has been one of my closest friends outside of Japan. Such a relationship started naturally through our common interest in cardiac arrhythmias, although he was mostly engaged in clinical studies whereas I was more deeply involved in basic electrophysiological experiments. However, what transformed this scientific relationship into a longlasting mutual friendship was undoubtedly his warm and charming personality. Dennis made an invaluable contribution to the field of cardiology by acting as the editor of *British Heart Journal* for 11 years, and I have always admired his insight and leadership. Hence, it was a real surprise when he told me in the autumn of 1990 that he was going to hand the editorship over to his successor. The news filled my heart with a deep emotion that we were perhaps witnessing a change of generation in the world of cardiology; in the past couple of years several other good friends of mine have retired both in Japan and abroad.

Because I am certain that others will comment on Dennis's achievement as a superb cardiologist and an able editor, I will concentrate on describing his contributions to the exchange of scientific information between the United Kingdom and Japan. I believe that the first of his many visits to Japan was in September 1978, when the Eighth World Congress of Cardiology was held in Tokyo. In a symposium on antiarrhythmic agents co-chaired by Dr Sloman and myself, Dennis spoke, as a pioneer, on the electrophysiological assessment of calcium ion antagonists in cardiac arrhythmias. Together with a lecture he gave in a post-congress conference, his well organised presentation and astute comments and discussions deeply impressed all of us.

Dennis was kind enough to invite me to give a lecture at Hammersmith Hospital in December 1978. His second visit to Japan in January 1979 was brief, but he left valuable advice on the development of a special model of an electrocardiograph. Dennis was also invited to be one of the overseas speakers in an international symposium in Kanazawa organised by Dr Iwa in the autumn of 1986. The title of his lecture at this symposium was "Current medical management of supraventricular arrhythmias".

Dennis made his most recent trip to Japan in October 1990. As president of the Japanese Society of Electrocardiology, I was pleased to ask Dennis to give the Hideo Ueda Lecture on the occasion of the society's Seventh Annual Scientific Session in Nagoya. The title of his lecture, "Preexcitation syndrome" was most appropriate and gratifying to Dr Ueda, who was the first to propose classification of type C Wolff-Parkinson-White pattern in 1957. The talk beginning with a historical overview of the studies on this syndrome and ending with a discussion on the latest developments in its non-pharmacological treatment was a superb educational exercise. In a post-congress symposium, Dennis discussed torsade de pointes, an arrhythmia that has attracted increasing attention worldwide since the publication of his paper in the *British Heart Journal* in 1976.

Through these visits Dennis has contributed so much to the international exchange of scientific knowledge. Not only that, he played a vital part in increasing the mutual understanding between Japanese and British cardiologists by making many new friends and renewing old friendships. Finally, it is my firm conviction that, because he is much too young to retire, Dennis will continue his global activities in research, teaching, and patient care for many years to come. I also hope that he will find numerous other opportunities to visit Japan to further our mutual friendship and academic cooperation.

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Medical historian

Dennis's contributions to the history of cardiology are as notable as his research into the clinical and academic aspects of heart disease. In fact in a way they are of greater note because only a few choose to "praise famous men and our fathers that begat us" and even fewer achieve excellence in that sphere. An interest in medical history seems to come early among its devotees. William Osler was 24 when he was attracted to the memory of Sir Thomas Browne and

Dennis was still a junior doctor in Cape Town when by chance he read a memoir of Willem Einthoven. It was written by the Russian physiologist A F Samojloff and it stimulated his interest in these two great pioneers of electrocardiography. Were it not for Dennis's historical research the life and work of Samojloff could well be unrecognised and much information about him lost. His excellent papers about him demonstrate well the gifts that Dennis has for careful enquiry, pursuit of detail, and personal friendship. He found Samojloff's one surviving son, got valuable photographs from Professor Chazov, and traced Samojloff's links with Paul White and Thomas Lewis.[1] Early in his career Dennis practised in Rhodesia (now Zimbabwe) and he must have been thrilled to find that a coworker of Thomas Lewis had been the first doctor in the pioneer town of Bulawayo in 1894. This was Dr Alfred Goodman Levy who was the subject of one of Dennis's first historical papers[2] in 1969. Another early and scarcely known paper[3] by him tells of the significant part that Jewish immigrants played in the development of Rhodesia and of Cecil Rhodes's appreciation of their importance in forming "his" country. Rhodes's closest associate was Sir Alfred Beit who founded the Beit Memorial Fellowships in medical research the first holder of one being Thomas Lewis in 1910.

Dennis has a keen eye for anniversaries, which is good because some would otherwise pass unnoticed. In 1981, the centenary of Lewis's birth, I was glad to have his request as the new editor of the *British Heart Journal* to write about Lewis's early work. Another contributor to that issue was Howard Burchell whose deep knowledge of cardiological history and wisdom in assessing past events has been so valuable both to Dennis and myself. I suspect it was Dennis's influence that led to Howard being asked to chair the memorable debate on the action of digitalis at the Withering bicentennial meeting in 1985. That was also the year in which with typical thoroughness he unmasked the myth that Withering had bought the foxglove secret from an "Old Mother Hutton".[4] Editors do not often write their own editorials but the *British Heart Journal* has had the double advantage of having editorials on historical topics written by its own editor. One in 1987[5] commemorated the fiftieth anniversary of the British Cardiac Society and it was thoughtful of Dennis to ask the society's first president, Dr Rae Gilchrist, to write a note and to mention that "it was written in his elegant hand . . . and ready for the printer as it stood". Another one in that volume was a fine review[6] of electrocardiography assessing the past and looking to the future. The golden jubilee of the *British Heart Journal* in 1989 was a natural occasion for Dennis to review[7] the journal's history and also to note perceptively that it was in addition the eightieth anniversary of the founding of *Heart*. He followed it with "The roots of modern British cardiology".[8] This was his George Burch Memorial Lecture and it reminds us of Dennis's international reputation as a medical historian. This reputation has been enhanced—to use what is I think Dennis's favourite verb—by the friendships he has created worldwide by his passion for cardiological history. The distinguished American medical historian Dr W Bruce Fye wrote to me recently about this and said "There are not many of us who enjoy this pleasant and enlightening interest. It is important that we encourage one another. Dennis Krikler has been so very helpful in my own career."

A couple of years ago when two collections of old photographs came into his hands Dennis seized the opportunity to create a new feature for the journal. He entitled it "Views from the Past" and he has written several nice vignettes to accompany the pictures of early workers such as Henry Dale, E H Starling, and Paul Rothschild. This series, probably unique among journals, will stand as a pleasant and enduring memory of his devotion to historical events during his fine editorship.

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1 Krikler DM. The search for Samojloff: a Russian physiologist in times of change. *BMJ* 1987;295:1624–7.
2 Krikler DM. Alfred Goodman Levy—Bulawayo's first doctor. *Cent Afr J Med* 1969;15:97–9.
3 Krikler DM. The pioneering Jews of Rhodesia. *The Wiener Library Bulletin* 1968; xxii N.S. 13:19–24.
4 Krikler DM. Withering and the foxglove: the making of a myth. *Br Heart J* 1985;54:256–7.
5 Krikler DM. Cardiac Club 1922: Cardiac Society of Great Britain and Ireland 1937. *Br Heart J* 1987;57:1.
6 Krikler DM. Electrocardiography then and now: where next? *Br Heart J* 1987;57:113–7.
7 Krikler DM. A 50 year perspective: the British Heart Journal. A title lost, but a reputation won. *Br Heart J* 1989;61:1–3.
8 Krikler DM. The roots of modern British cardiology. *Br Heart J* 1989;62:230–4.

Envoi

Dennis Krikler retires after 11 years as editor of the *British Heart Journal*. As the previous editor, I recall handing over to him the seal of office and thereby easing my mind from the anxiety for the journal's continuing prestige and prosperity. This confidence was borne from sharing with him the editorial desk for the previous six years. At that time, I was surrounded by experienced editorial talent and soon all came to share my conviction that the journal's future was assured.

The evidence of many years testifies that successful editors are not so much appointed as obey a vocational call to office and so willingly forgo many professional and material deserts. Krikler had no option but to listen to this summons. Within months of editorial evolution, he developed that form of literary paternalism common in strongly motivated editors. He rejoiced in responsibility, provided guidance and encouragement yet he avoided usurping liberty of choice and individual responsibility and other evils of over-zealous fatherly direction which have given literary paternalism a bad name.

Krikler promptly accepted the challenge of maintaining the literary, ethical, and communication standards set by his predecessors, Evan Bedford, Maurice Campbell, and Kenneth Shirley Smith. His period in office coincided with the most influential advance in the management of coronary heart disease, thrombolysis, and with the use of molecular techniques in diagnosis and treatment as well as the maturity of surgical treatment. The editorial office was flooded with multinational writings and challenged the editor's qualities of prudence and wisdom. With the prerequisite of all good leaders, Krikler had surrounded himself with a hand-chosen editorial committee who, sharing the same critical faculty, sorted out the few grains of wheat from the chaff.

Krikler's personality fostered close friendship with some of the most creative personalities in the field of contemporary medical communication, Stephen Lock, Arnold Relman of the *New England Journal of Medicine*, Simon Dack of the *Journal of the American College of Cardiology*; Sylvan Weinberg appointed him to the editorial committee of ACCEL (American College of Cardiology Extended Learning) and he became one of the best known voices on the successful ACCEL tapes.

Part-time medical editors commonly follow a general trend of relegating their duties to a low priority. Krikler was a notable exception; he promoted his function as a communicator to a prominent site in a highly committed clinical programme. He was happy in the company of full-time editors and when the Vancouver Group was formed (the International Committee of Medical Journal Editors), he made full use of the progress made in the clarification of problems faced by medical editors. The journal's two face-lifts were facilitated by his vision, the first meant discarding the deep crimson cover so beloved by the journal's founders, and the second called for the enlargement of the page size and format to conventional dimensions. Both of these changes meant a break with the old order, not an easy emotional volte-face for a man with strong attachments to tradition and sentiment. Yet his personal philosophy demanded a proper place for these qualities, well below precision and purity of expression. He was assistant editor when the term "dysrhythmia" first appeared in an overseas journal. Both he and I felt it a duty to discourage this unhappy neologism. I gladly accepted Dennis's offer to write an appropriate editorial. This curbed, but did not suppress, the unfortunate term.

As Dennis Krikler takes his leave, I can promise him that reflecting in tranquillity on the past 11 years, he will be armed by the satisfaction of successful service to the journal. The journal's loss, however, is to a great extent compensated by the inspired choice in his place of a highly motivated and distinguished pathologist, Professor M J Davies. He has ahead of him a period of challenge and stimulation. The British Cardiac Society is to be complimented on its choice.

WALTER SOMERVILLE
Editor, *British Heart Journal* 1973–80

Br Heart J 1992;67:16–24

REVIEWS

Vagaries of acceleration dependent aberration

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The earliest electrocardiogram illustrating bizarre intraventricular conduction of supraventricular impulses was published by Sir Thomas Lewis in 1910.[1] In a subsequent communication Lewis labelled this form of abnormal conduction "aberration" and the ventricular complexes as "aberrant beats."[2] In that same paper he also proposed a mechanism for the aberration, namely ". . . disturbances of conduction in the smaller branches of this system and it is held that definite branches are affected in this manner, though these branches cannot be identified at the present time". The underlying milieu for aberration proposed by Lewis stood the tests of further observation and experimentation. Altered, asynchronous conduction has been demonstrated for all segments of the His-Purkinje system as well as the Purkinje-myocardial junctional areas and, rarely, as a result of preferential atrioventricular and, perhaps, His bundle conduction. The mechanisms responsible for initiating the conduction alterations are, however, even more complex as attested to by the vast number of published reports, both basic and clinical, on aberrancy that has been generated since Lewis' initial observations.

In 1983, on the occasion of the 75th anniversary of Sir Thomas Lewis' description of aberration, Dr Dennis Krikler, Editor of the *British Heart Journal,* invited an editorial on that subject.[3] As our contribution to this Festschrift issue of the British Heart Journal honouring Dr Krikler, we have elected to continue that discussion and focus on the vagaries of acceleration dependent aberration. The subject is particularly well suited to Dr Krikler's long time interest in the history of cardiology and, in particular, in tracing the development of concepts in electrophysiology.

We have collated scattered reports on eccentric forms of acceleration dependent aberration and on mechanisms that could explain the vagaries proposed in the hope that further interest in the mechanisms underlying aberration will be stimulated. The material comes from our files and our earlier publications.

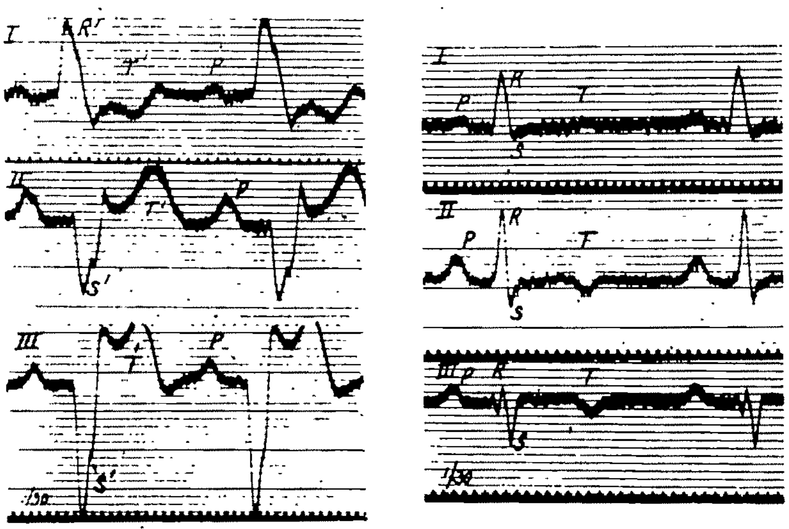

Fig 18.

Fig. 19.

Fig. 18. Curves taken from the three leads in a case of aortic disease during a febrile attack. They show defective conduction along the right division of the auriculo-ventricular bundle (see Fig. 16).

Fig. 19. Curves from the same patient, taken a day later and during the subsidence of the fever. The ventricular portions of the curves have changed profoundly; there is now no evidence of bundle defect, but of preponderance of the left ventricle.

Figure 1 Earliest example of acceleration dependent aberration. (Reproduced from Lewis T. The mechanism and graphic registration of the heart beat. London: Shaw and Sons, 1920:125.)

Background and observations

In 1913, Lewis published two electrocardiograms illustrating the disappearance of bundle branch block with slowing of the heart rate (fig 1).[4] Although the tracings were recorded on different days, they probably are the earliest example of acceleration dependent aberration.

The classic manifestation of acceleration dependent aberration is the appearance of aberration at a critical cycle length reached in the course of an increase in heart rate, and normalisation of conduction with slowing of the heart rate to the point that the RR cycle is again longer than that at which aberration was initiated (fig 2).[5]

While the predictability of the relation between rate and aberrancy is characteristic for acceleration dependent aberration, there are exceptions to this heart rate dependency that we will refer to as vagaries or eccentric forms of acceleration dependent aberration, an example of which also was first reported by Lewis.[6] The vagaries will be divided into two groups: *Group 1*—unexpected normalisation of conduction when aberration would be expected to continue—and *Group 2*—unexpected appearance or persistence of aberration under conditions in which it would not be expected. Examples under each group are presented and discussed below.

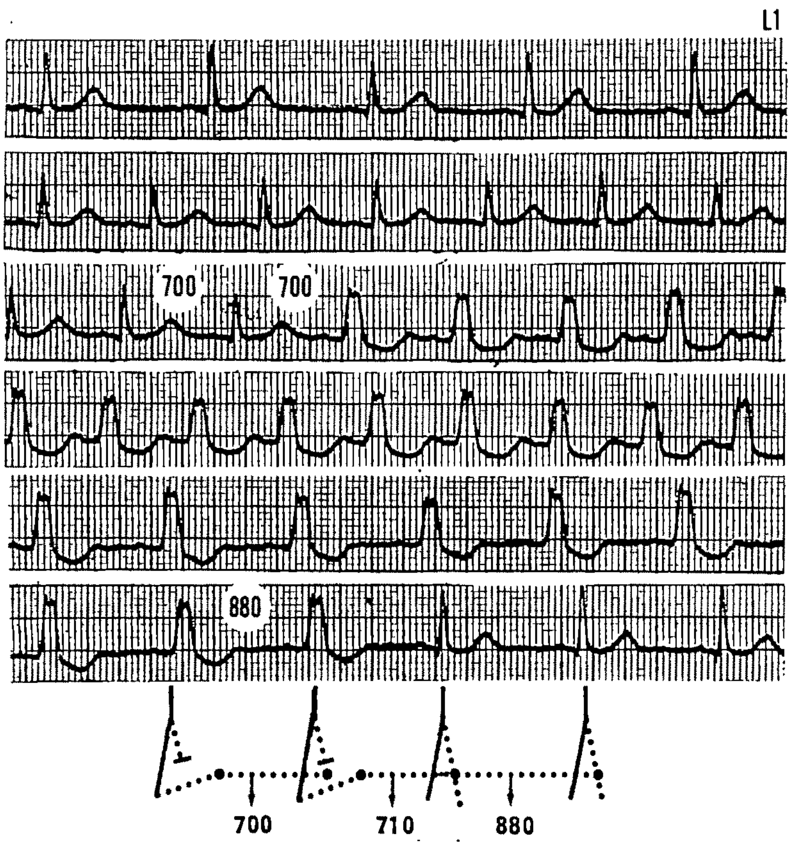

Figure 2 Acceleration dependent aberration with unexpected (1) persistent aberration at cycles longer than the critical cycle due to transseptal concealed conduction shortening the bundle branch to bundle branch interval to a critical cycle of 700 ms and (2) absence of shortening of the critical cycle when compared with the immediately preceding cycle. (Reproduced from Fisch C, Zipes DP, McHenry PL. Rate dependent aberrancy. Circulation 1972;48:714 by permission of the American Heart Association, Inc.)

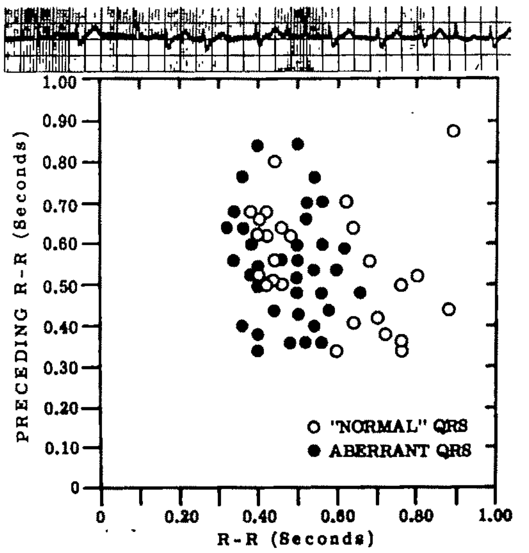

Figure 3 Relation of the coupling interval of the normal and aberrant QRS (abscissa) to the preceding RR cycles (ordinate). The presence of paradoxically normal QRS at coupling intervals of 0·40 to 0·50 s is dependent on the preceding RR measuring approximately 0·50 to 0·80 s. This dependency on duration of the preceding cycle suggests a shift of the supernormal period to the right with the longer preceding RR intervals and the location of the supernormal period at 0·40 to 0·50 s after the QRS. (Reproduced with permisson from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger. 1990:243,244.)

GROUP 1

Normalisation with abrupt shortening of the cycle length

One of the most common vagaries of acceleration dependent aberration is normalisation of intraventricular conduction at cycles shorter than those of the aberrantly conducted complexes. This occurs with an abrupt shortening of the RR interval such as that which may be seen with atrial fibrillation[7] (figs 3 and 4), single atrial premature complexes (fig 5), runs of atrial premature complexes, or 3:2 atrioventricular block.

The most likely mechanism responsible for unexpected normalisation of conduction with abrupt shortening of RR interval is conduction during the supernormal period of His-Purkinje recovery.[7,8] This is supported by the fact that there is a constant, or rarely a shorter, H-V interval,[9] and that the coupling of the normally conducted impulses, in most cases, varies directionally with the preceding bundle branch to bundle branch interval the duration of which may be dependent on the presence or absence of concealed transseptal conduction from the contralateral bundle (figs 3 and 5).[8,10–12] In a unique example in which the His bundle electrogram was recorded, the H-V interval of the supernormally conducted impulse remained normal, or was shorter than the H-V of the aberrantly conducted impulses (fig 4).[9]

Equal delay of conduction in the bundle branches has been suggested as an alternative to supernormality as an explanation for unexpected normalisation of the QRS at short cycles. The finding that would support this mechanism for paradoxical normalisation would be prolongation of the H-V interval recorded simultaneously with normalisation of the intraventricular conduction. Such observations have, as yet, not been reported. Prolongation of the PR interval commonly accompanies the normal QRS, but this may be an expression of atrioventricular nodal rather than bundle branch prolongation.

Normalisation during an accelerating tachycardia

Occasionally intraventricular conduction becomes normal after several cycles of acceleration dependent aberration.

While the initial aberration in fig 6 represents acceleration dependent aberration due to bundle branch refractoriness, normalisation of conduction is most likely due to a gradual shortening of the bundle branch refractory period over several cycles. This may be a normal adaptation of action potential to rate or possibly a result of an increase in the concentration of circulating catecholamines. Increased speed of conduction in the contralateral bundle branch or an equal delay in both bundles also are possible, but, as discussed above, these are unlikely mechanisms for normalisation of conduction.

On rare occasions, aberration disappears in the course of a gradual acceleration of heart rate, a phenomenon that has been observed during stress tests (fig 7). In such instances a 2:1

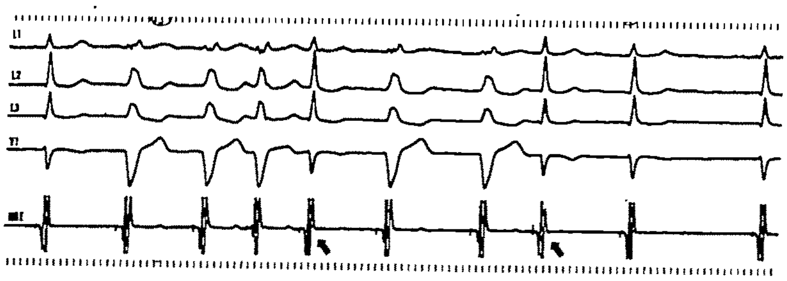

Figure 4 Normalisation of QRS at paradoxically short cycles with a slight shortening of the H–V interval supporting supernormal His-Purkinje conduction as the cause of the normalisation. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:241.)

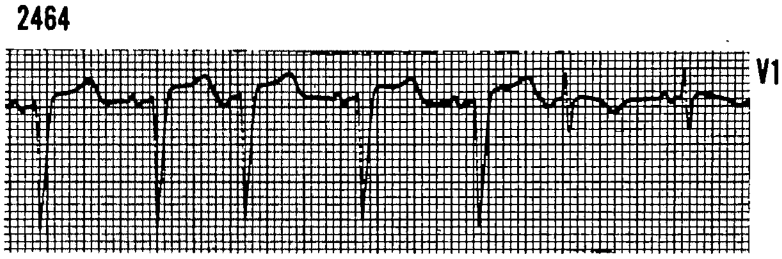

Figure 5 Atrial premature complex with a paradoxically normal QRS is followed by a normally conducted sinus impulse whereas the atrial premature complex with aberration is followed by an aberrant QRS. The latter is most likely due to concealed transseptal conduction of the atrial premature complex shortening the bundle branch to bundle branch interval resulting in acceleration dependent aberration. (Reproduced with permission from Fish C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:233.)

bundle branch block may precede or follow normalisation of conduction.

To the best of our knowledge the record reproduced in fig 8 is the only known example of paradoxical normalisation of conduction after a long preceding cycle when, according to the Ashman phenomenon, aberrant conduction would be expected[13 14] rather than the normal conduction noted in this tracing. It is most likely that prolongation of the transmembrane action potential after the long pause fortuitously allows for conduction during the supernormal period of recovery.

Intermittent normalisation and aberration

Bundle branch block and normal conduction may be recorded intermittently during a regular rhythm. The ratio of bundle branch block to normal conduction may vary from a sporadic bundle branch block to 2:1 or higher ratios of bundle branch block to the normally conducted QRS complexes (figs 9 and 10).

The mechanisms proposed to explain the intermittent bundle branch block include: (*a*) small changes in cycle length not recognisable in the electrocardiogram, (*b*) block of the impulse above the bundle branch lesion responsible for the bundle branch block allowing for a prolonged recovery time,[15] (*c*) Wenckebach conduction in the bundle branch,[16] (*d*) deceleration and acceleration dependent bundle branch block,[17] and (*e*) supernormal conduction.[9] The two latter mechanisms may be facilitated by concealed transseptal conduction[11 18] (fig 10) that alters the duration of the bundle branch to bundle branch interval, the duration of the action potential, and thus the relative position of the supernormal period of recovery.

Phase 4 depolarisation has been suggested as a mechanism for 2:1 bundle branch block. With phase 4 depolarisation, it has been postulated that after a normal QRS the left bundle branch to left bundle branch interval is relatively "long" and thus results in bundle branch block. In the presence of the left bundle branch block, an impulse conducts along the right bundle branch, traverses the septum, and reaches the left bundle branch after some delay. The result is a "short" left bundle branch to left bundle branch interval, dissolution of phase 4 depolarisation, and as a result normal conduction.[17] Although electrocardiographic observations tend to support phase 4 depolarisation as a possible mechanism of deceleration dependent aberration,[19 20] some believe, based on cellular observations, that deceleration dependent aberration is the result of "complex oscillatory changes in membrane properties of depressed bundle branch Purkinje fibres during diastole."[21]

Another mechanism that could explain 2:1 bundle branch block is that block above an area of injury occurs so that the left bundle branch to left bundle branch interval encompassing the normal QRS is equal to two sinus cycles, allowing for bundle branch recovery and normal conduction, or, alternatively, it is also possible that delay of conduction above an area of injury could allow for recovery of excitability of an injured area and/or other electrophysiological parameters necessary for normal conduction. This mechanism resembles the gap phenomenon. For these two latter mechanisms to be possible, the bundle branch must not be activated retrogradely. Should retrograde conduction take place, prolonged recovery is no longer possible.

GROUP 2

Onset of aberrant conduction without a recognisable shortening of RR interval

This is a common phenomenon (fig 2). While

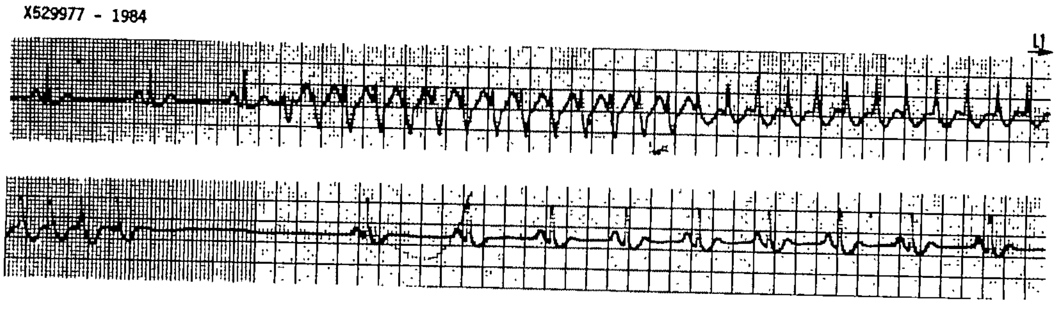

Figure 6 Normalisation of acceleration dependent aberration without any demonstrable change in heart rate. The most likely mechanism is shortening of the refractory period in response to the tachycardia. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:69.)

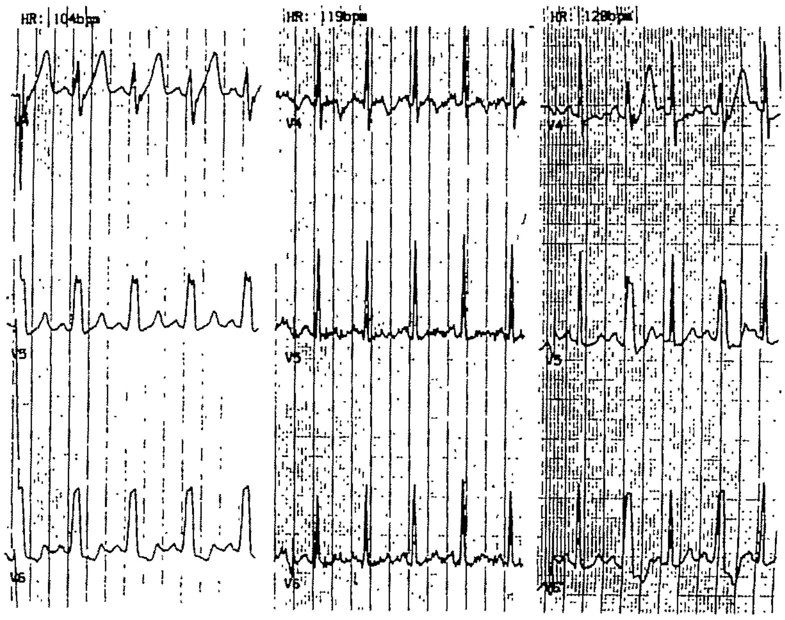

Figure 7 Paradoxical normalisation of the QRS in course of acceleration of the heart rate during a stress test. Mechanisms suggested as an explanation for the normalisation include increase of sympathetic activity, catecholamine release, supernormal conduction, and physiological shortening of the refractory period.[9]

there is no doubt that the aberration is a function of acceleration of the heart rate, this may become obvious only when long records are available to allow the gradual shortening of the cycle length to be recognised. Failure to appreciate shortening to the "critical" aberrancy-inducing RR interval reflects a limitation of electrocardiographic technology; aberration may be a function of small changes of the cycle, often measured in milliseconds, and such changes may not be recognisable in the surface electrocardiogram. It is also possible under certain conditions that with gradual acceleration of the heart rate the refractory period inappropriately lengthens, resulting in conduction delay or block without the need for shortening of the "critical" cycle.

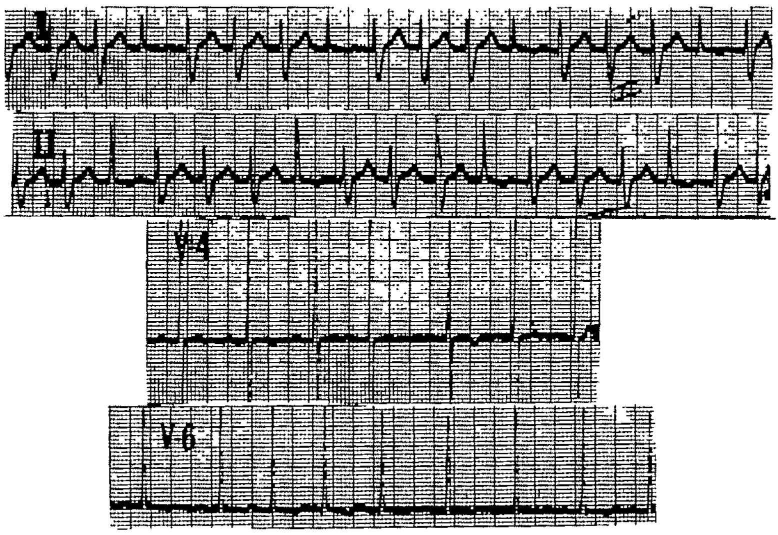

Figure 9 Intermittent normalisation of conduction during a regular rhythm with acceleration dependent aberration. The fact that the aberration represents acceleration dependent aberration is proved by normalisation of conduction with an 80 ms prolongation of the cycle in lead V4.

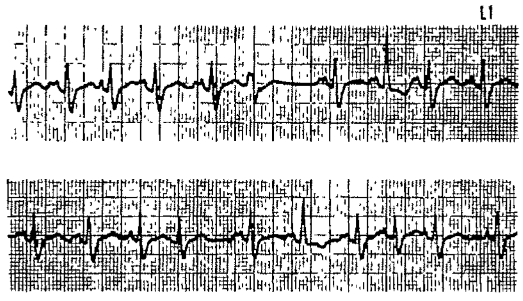

Figure 8 Paradox of normal conduction after a long RR cycle when according to the Ashman phenomenon aberration would be expected. The most likely explanation is supernormal conduction made possible by the prolonged recovery period with a shift of the supernormal period to the right. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:236.)

Persistence of aberration at a cycle longer than the "critical" cycle

This phenomenon also is a frequent finding in clinical electrocardiograms (fig 2). The most likely mechanism is concealed transseptal conduction that shortens the bundle branch to bundle branch interval. As a result of transseptal conduction the actual bundle branch to bundle branch interval is shorter than the manifest QRS to QRS interval (fig 2). Not only is the bundle branch to bundle branch interval altered but the duration of the subsequent refractory period also is changed. Transseptal conduction has been shown experimentally in the dog[10 11] and in humans.[12 22 23] Whereas concealed transseptal conduction alone may shorten the bundle branch to bundle branch cycle sufficiently to result in acceleration dependent aberration and its persistence, often it combines with other mechanisms to propagate aberrancy at cycles longer than the "critical" cycle. In some patients the discrepancy between the "critical" cycle and cycle at which normal conduction resumes may be on the order of 210 ms, an interval longer than could be explained simply on basis of the transseptal conduction.[24]

Alternate mechanisms for persistence of aberration may be "fatigue" and overdrive suppression, both of which are a function of increased rates. "Fatigue" is a concept proposed by Shearn and Rytand in 1953 to explain the unexpected persistence of aberration with slowing of the rate[5] and is a descriptive phenomenon, the cellular basis for which is unclear. It is an attractive and logical concept that suggests that a persistently accelerated rate, sufficiently rapid to induce acceleration dependent aberration, alters the electrolyte milieu and that such alterations may persist over several cardiac cycles, some longer than the "critical" cycles at which aberrancy was initiated.

Overdrive suppression of conduction, first demonstrated by Scherf in the dog,[25] is manifest by the appearance of bundle branch block upon cessation of a rapid heart rate or, on occasion, after a single early excitation or stimulus (fig 11). Overdrive suppression of bundle branch conduction is in many ways

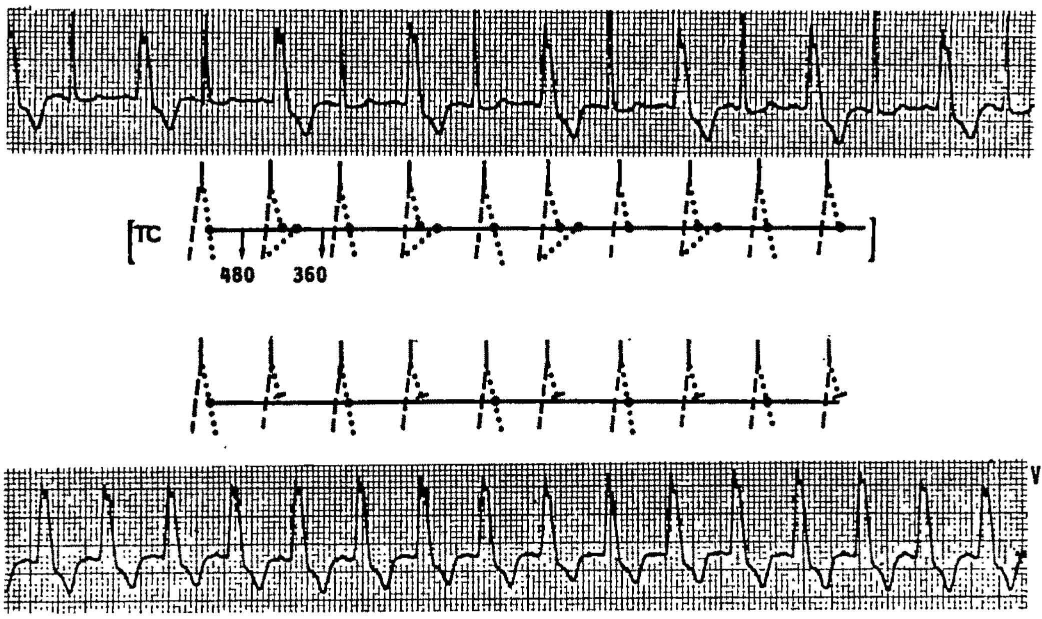

Figure 10 2:1 Left bundle branch block followed by persistent aberration, the result of a slight acceleration of the heart rate. TC, transseptal concealment.

similar to overdrive suppression of atrioventricular conduction. The duration of suppression depends on the rate of the overdriving impulse: the higher the rate the longer the recovery time. Overdrive suppression after ventricular tachycardia is manifest by a gradual normalisation of bundle branch conduction in the face of acceleration of the sinus rate (fig 11).[26] It is a phenomenon which, unlike "fatigue", could explain aberration after a single early excitation or stimulus. The exact electrophysiological basis responsible for overdrive suppression is uncertain.

Unexpected persistence of aberration induced by the Ashman phenomenon

A relatively frequent observation first recorded by Lewis[6] is the persistence of aberration once initiated by sudden prolongation of the refractory period in response to a long cycle—the Ashman phenomenon (figs 12 and 13). The aberration persists at cycle lengths identical to those manifesting normal conduction.

Whereas the Ashman phenomenon is responsible for aberration of the first complex,[13 14] persistence of the aberration may be due to delayed concealed transseptal conduction from the left to the right bundle branch resulting in shortening the right bundle branch to right bundle branch interval and thus initiation of acceleration dependent aberration. A constant heart rate and a fixed relation of transseptal conduction to anterograde conduction in the contralateral bundle branch are critical for perpetuation of the aberration.

Appearance of aberration during a regular heart rate

Acceleration dependent aberration may appear after several normally conducting impulses during a regular heart rate (fig 14). The appearance of aberration without a demonstrable change in the heart rate is most likely due to gradual prolongation of either voltage or the time dependent refractoriness (fig 15). Inappropriate restitution of ionic concentrations may contribute to the time dependent refractoriness and may to some extent also explain "fatigue" and overdrive suppression (see above).

Aberration secondary to gradual delay of bundle branch conduction

Gradual delay of bundle branch conduction (fig 16), evidenced by a gradual widening of the QRS, has been equated with type I, Wenckebach, second degree bundle branch block.[16 27] Similarly, intermittent normalisation of bundle branch conduction may represent concealed Wenckebach conduction (fig 9). Once the delay of bundle branch conduction reaches a critical point and a complete bundle branch block is inscribed, any further delay of bundle

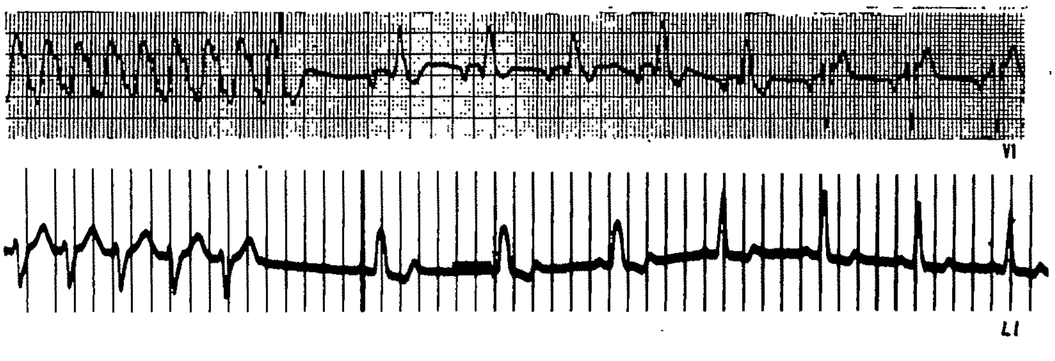

Figure 11 Overdrive suppression of bundle branch conduction by ventricular tachycardia. (Reproduced from Fisch C. Bundle branch block after ventricular tachycardia: a manifestation of "fatigue" or "overdrive" suppression. J Am Coll Cardiol 1984;3:1562 by permission of the American College of Cardiology.)

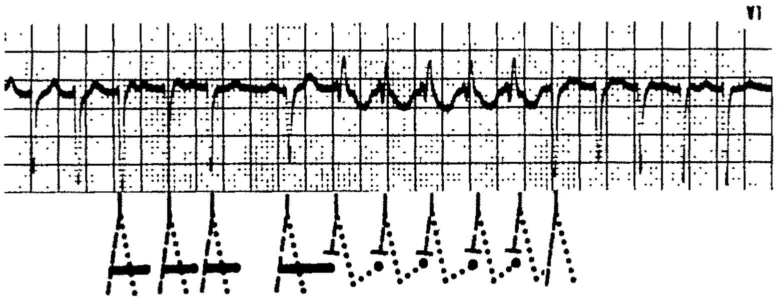

Figure 12 Aberration initiated by the Ashman phenomenon and perpetuated by concealed transseptal conduction that shortens the bundle branch to bundle branch interval thus initiating acceleration dependent aberration. Solid bar denotes right bundle branch refractory period, and broken and dotted lines show the right and left bundle branch block respectively with transseptal conduction of the latter. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias: from deductive analysis to laboratory confirmation—twenty five years of progress. J Am Coll Cardiol 1983;1:206.)

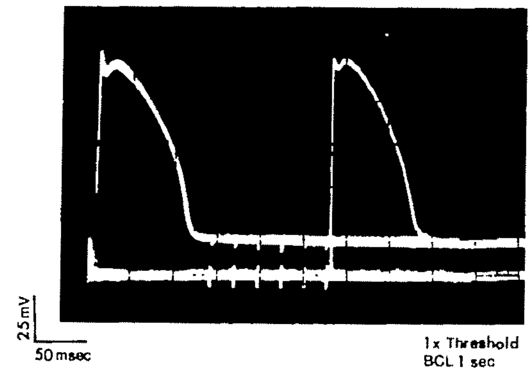

Figure 15 Time dependent refractoriness is illustrated by failure of the stimulus to elicit a response after full recovery of transmembrane action potential. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febinger, 1990:60.)

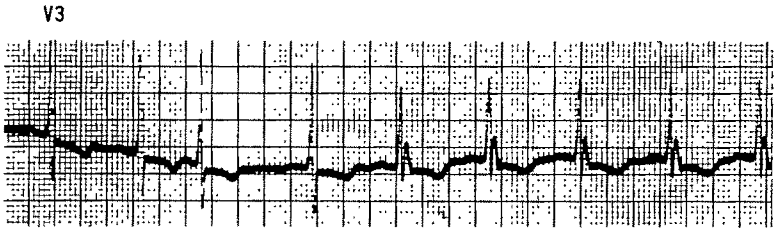

Figure 13 Right bundle branch initiated by the Ashman phenomenon and perpetuated by acceleration dependent aberration with the obligatory shorter bundle branch to bundle branch interval being the result of concealed transseptal conduction. The paradox of normal conduction of the atrial premature complex is probably due to conduction during the supernormal period (Reproduced with permission from Knoebel SB, Fisch C. Concealed conduction. In: Fisch C, ed. Complex electrocardiography I. Philadelphia: FA Davis, 1973.)

branch conduction cannot alter the QRS duration and thus will go unrecognised.

Aberration and the "crossover" phenomenon
The paradox of left bundle branch block at shorter coupling intervals and of right bundle branch block at longer coupling intervals (fig 17) has been recognised for years.[28] It is often referred to as the "crossover" phenomenon and reflects the paradox of a longer refractory period of the left bundle branch at short coupling intervals and a longer refractory period of the right bundle branch at longer coupling intervals. The mechanism responsible for this phenomenon is unclear but is probably secondary to injury.[29]

Aberrant conduction after premature complexes or pauses
Aberrant conduction may terminate a compensatory pause after an atrial premature complex while, paradoxically, normal conduction may follow a shorter compensatory pause induced by a ventricular premature complex (fig 18). The most likely mechanism for aberration after the atrial premature complex is concealed conduction of the atrial premature complex into the bundle branch thus shortening the bundle branch interval as discussed above. A possible but unlikely mechanism for aberration after an atrial premature complex is diastolic depolarisation. Phase 4 depolarisation is, however, incompatible with bundle branch block during sinus rhythm at considerably shorter cycles, unless one accepts the presence of acceleration and deceleration aberration.

In the presence of multiform ventricular premature complexes a compensatory pause following one pattern of ventricular premature complex may be terminated with aberration while the compensatory pause of a different form of ventricular premature complex may terminate with a normally conducting QRS (fig 19). The most probable explanation for such observations is that concealed conduction into the bundle branch with shortening the bundle branch interval occurs with one type of ventricular premature complex and not the other.

Rarely, intermittent supraventricular tachycardia is interrupted by pauses that are followed by aberrant conduction at a rate identical with that of the normally conducted complexes (fig 20). The mechanism for the aberration in such cases is unclear. One can postulate that the first aberrant QRS after the pause is due to diastolic depolarisation and that propagation of aberration is due to concealed transseptal conduction from the contralateral bundle branch thus shortening the bundle branch to bundle branch interval.

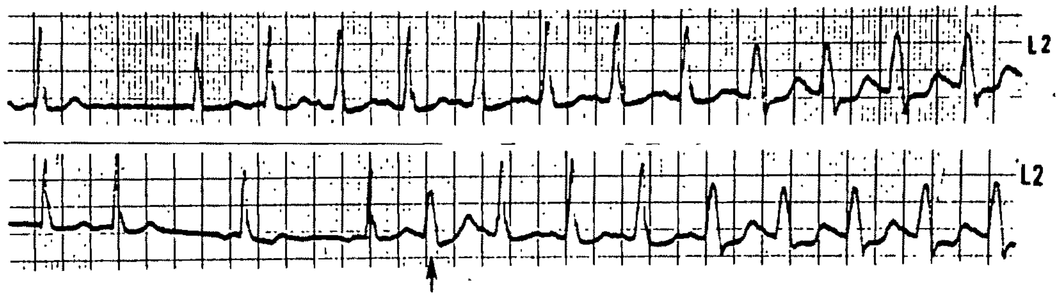

Figure 14 Appearance of a gradually increasing aberration without any demonstrable change in heart rate is recorded in the top trace. The Ashman phenomenon and acceleration dependent aberration with a progressive widening of the QRS is illustrated in the bottom trace. The most likely mechanism of the acceleration dependent aberration is an inappropriate, gradual prolongation of the refractory period. (Reproduced from Fisch C, Zipes DP, McHenry PL. Rate dependent aberrancy. Circulation 1973;48:714 by permission of the American Heart Association, Inc.)

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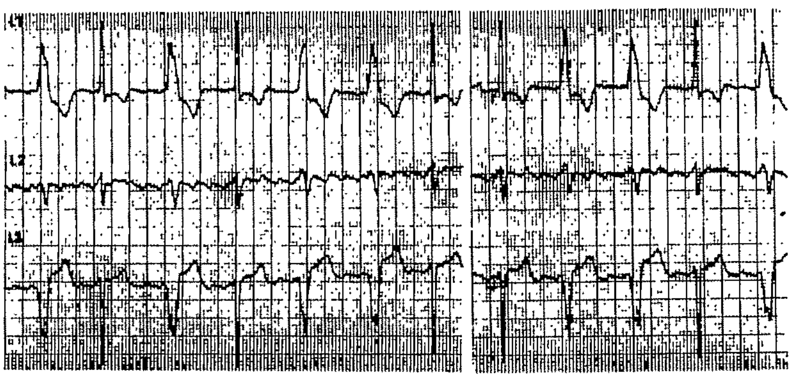

Figure 16 Progressive delay of left bundle branch conduction suggesting type I, Wenckebach, bundle branch conduction.

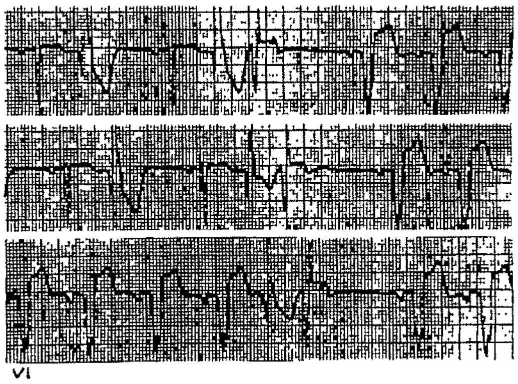

Figure 18 Concealed conduction of the atrial premature complex into the left bundle branch with shortening of left bundle branch to left bundle branch interval is responsible for the paradox of left bundle branch block after pauses longer than the pauses that follow ventricular premature complexes and which are terminated by a normal QRS. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:81.)

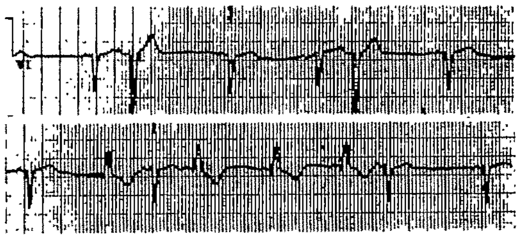

Figure 17 This figure shows (1) right bundle branch acceleration dependent aberration (2) paradox of normal conduction of atrial premature complexes, and (3) APC with left bundle branch block conduction reflecting the crossover of the refractory periods of the right and left bundle branch.

Acceleration dependent aberration appearing at slow heart rates

One of the most intriguing vagaries of acceleration dependent aberration is its appearance at extremely slow heart rates. While the vast majority of patients manifest acceleration dependent aberration at cycles longer than 750 ms, aberration at intervals as long as 1000 ms and occasionally as long as 1800 and 2000 ms have been recorded (fig 21). Although significant prolongation of the action potential duration has been recorded in abnormally functioning Purkinje fibres,[30-32] aberration at such strikingly slow rates cannot be readily explained by simple prolongation of recovery of transmembrane potential (voltage dependent refractoriness). Time dependent refractoriness can be postulated (fig 15). It is also possible that a delay or block of conduction in the His-Purkinje system can result because of an abnormal state of the His-Purkinje system, with a reduction of diastolic potential,[33] coupled with gradual diastolic depolarisation and slowing of the upstroke velocity and a shift in threshold toward zero. Injury of the His-Purkinje system may cause such changes.[29]

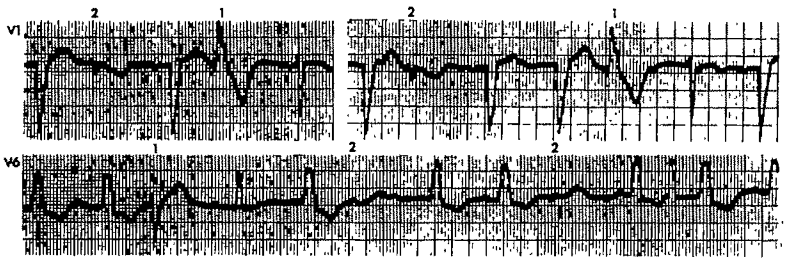

Figure 19 Concealed conduction of ventricular premature complex 2 into left bundle branch shortens the bundle branch to bundle branch interval and consequently the compensatory pause is terminated by a sinus impulse with left bundle branch block. Ventricular premature complex 1 does not conceal into the left bundle branch, is followed by a left bundle branch to left bundle branch interval that is longer than that following ventricular premature complex 2, and is therefore terminated with a normal QRS. (Reproduced from Fisch C, Zipes DP, McHenry PL. Rate dependent aberrancy. Circulation 1973;48:714 by permission of the American Heart Association, Inc.)

Another mechanism for aberration at unexpectedly long cycles may be concealed conduction into a bundle branch block. This has been observed with atrial and ventricular premature complexes. Similarly, during atrial fibrillation, persistence of aberration at long cycles may be due to concealed conduction of fibrillatory waves into a bundle branch as mentioned above.

Discussion

While a strong case can be made in favour of one or another mechanism for aberration in any given setting and some have been documented experimentally, the fact remains that most explanations still are based in deductive reasoning and extrapolations from the behaviour of the myocardium as reflected in the electrocardiogram by the P and QRS and, occasionally, the His-bundle electrocardiogram. It is almost certain that some of the conclusions so arrived at are in error. Many of the basic, cellular processes responsible for aberration remain to be elucidated. More sophisticated techniques for recording activation sequences and local action potential characteristics in the human will be required to allow more precise assessment of the mechanism for aberrancy under physiological and pathological conditions. However, for the purpose of giving structure to the observations presented above, it may be helpful to review some concepts about aberrancy that have developed since Lewis's original observations.

There is strong evidence indicating that acceleration dependent aberration is a marker of heart disease. While the heart disease may not be clinically evident initially, clinical signs

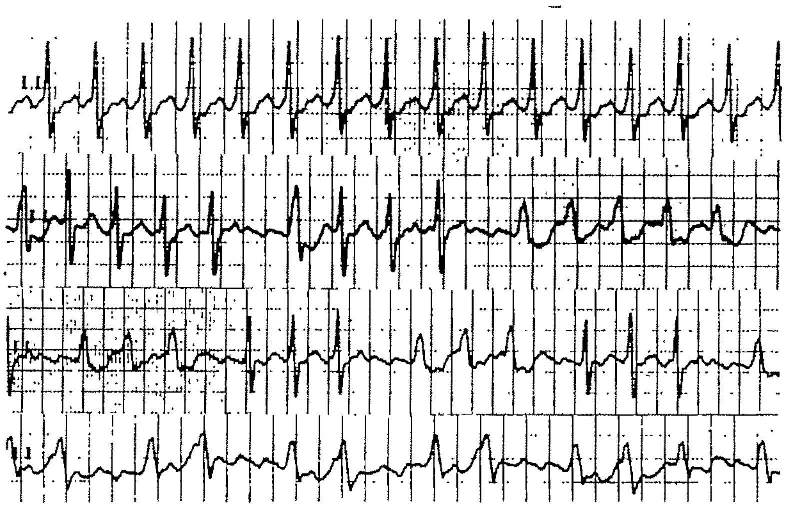

Figure 20 Aberration follows paradoxically longer cycles and continues at a rate identical to that of the normally conducted complexes.

of heart disease usually appear with time. Evidence supporting the association between acceleration dependent aberration and heart disease includes: (*a*) the high prevalence of heart disease in association with the acceleration dependent aberrancy, (*b*) the appearance of aberrancy at surprisingly slow rates, (*c*) the predominance of left bundle branch block aberrancy, (*d*) the frequent coexistence of acceleration with deceleration dependent aberration, the latter being a sign of heart disease, (*e*) the occasional appearance of acceleration dependent aberration after several equal RR cycles indicating inappropriate refractory period stability and/or abnormal electrophysiological properties, (*f*) independence from the duration of the preceding cycle (fig 22).

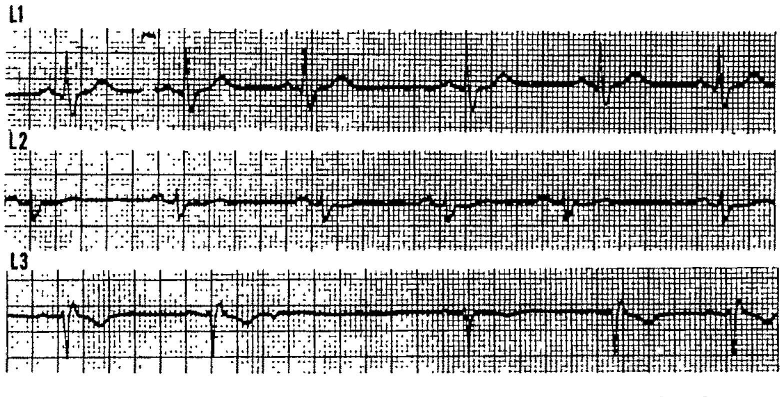

Figure 21 Aberration at cycle lengths varying from 920 to 1250 ms. The fact that aberration is acceleration dependent is documented by normalisation of conduction after the long compensatory pause induced by the blocked atrial premature complex. Aberration at such long cycles may be due to time dependent refractoriness, to injury,[29] or a combination of the two. (Reproduced with permission from Fisch C. Electrocadiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:62.)

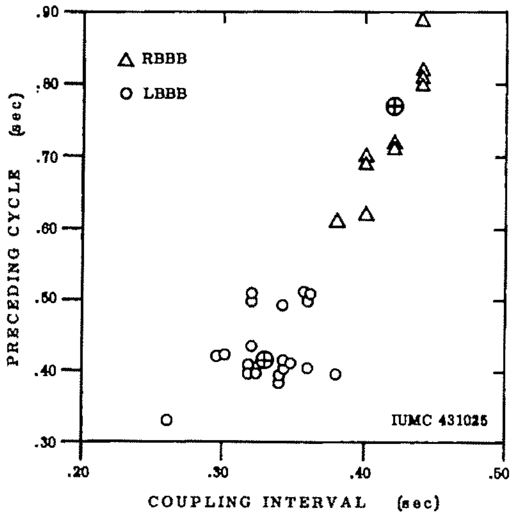

Figure 22 Relation of the coupling interval (abscissa) to preceding cycle length (ordinate) of the right and left bundle branch block aberration. Whereas left bundle branch block is independent of the duration of preceding cycle, right bundle branch is dependent on the duration of the preceding cycle. The right bundle branch block follows long preceding cycles in keeping with the Ashman phenomenon. It is possible that the considerable shorter coupling interval of the left bundle branch as compared with that of the right bundle branch reflect the crossover phenomenon of the refractory periods of the bundle branch. (Reproduced with permission from Fisch C. Electrocardiography of arrhythmias. Philadelphia: Lea and Febiger, 1990:66.)

Acceleration dependent aberration differs from physiological or "expected" forms of aberration as follows: "expected" aberration is seen in normal hearts; "normal" aberration is elicited by a premature impulse or stimulus and rarely, if ever, by a gradual acceleration of the rate because atrioventricular refractoriness will usually exceed His-Purkinje refractoriness thus precluding aberration; physiological aberration is nearly always of right bundle branch block pattern; coupling of a stimulus that elicits physiological aberration is quite short so that the stimulus occurs during the recovery of the action potential and the aberration can be readily explained by voltage dependent refractoriness; and the presence or absence of aberration is dependent on the duration of the preceding cycle length (fig 22). Because of the differences between aberration that may be present in the normal heart and acceleration dependent aberration which is nearly always an expression of an abnormal state, the two forms should be considered to be different phenomena if interpretation of the data dealing with aberration is to be meaningful.

Proposed mechanisms for acceleration dependent aberration as presented above include: (*a*) prolongation or failure of the action potential to shorten appropriately in response to an increase in heart rate, creating the milieu for voltage dependent refractoriness,[34] (*b*) refractoriness persisting after completion of repolarisation (time dependent refractoriness) or, (*c*) myocardial injury involving one of the bundle branches or fascicles resulting in partial depolarisation of cells within the affected bundle creating conduction delay or block that is independent of refractoriness.[29] Local action potential alterations also may electrotonically affect cells more proximal in the conduction system creating slowed conduction or block at that level.

While it is possible that in pathological states voltage or time dependent refractoriness may be altered sufficiently to be responsible for acceleration dependent aberration, and, while functional conduction disturbances have been shown to be favoured at low basic heart rates,[35] it is unlikely that either could account for aberration at cycle lengths of 1000 ms or longer, a not infrequent finding in acceleration dependent aberration. In such instances, disturbances of conduction are more likely to be secondary to alterations in action potential characteristics such as phase 4 depolarisation, slowing of the upstroke of phase 0, or reduction of threshold potential due to electropathology. A unifying concept could, therefore, be that injury to the conduction tissue, at diverse levels, is the basic defect that underlies acceleration dependent aberration.

When the vagaries of acceleration dependent aberration are under consideration still other mechanisms or combinations of mechanisms need to be invoked. Examples of these are presented above and include: (*a*) shortening of the bundle branch to bundle branch cycle without change in the manifest QRS to QRS cycle secondary to concealed transseptal conduction[12 17 23] or concealment of atrial and ventricular premature complexes into the bundle branches, (*b*) local injury enhanced by acceleration of the heart rate and a resultant depression or block of conduction manifesting as fatigue,[5] or overdrive suppression,[25 26] (*c*) conduction during the supernormal period of recovery,[9] (*d*) block above the area of injury allowing for bundle branch recovery, (*e*) "crossover" of the refractory period duration of right and left bundles,[28 36] (*f*) equal prolongation of bundle branch conduction, (*g*) diastolic (phase 4) depolarisation,[17 33] or, (*h*) Wenckebach block in a bundle branch.[16 27]

Aberration under normal physiological conditions, acceleration dependent aberration and its vagaries, and the similarities and differences between the various "normal" and "abnormal" forms of aberrancy provide a model for understanding electrophysiological functioning that is unequalled by any other concept. Even if basic cellular and intracellular mechanims for electrophysiological alteration are eventually totally understood there will continue to be the need for an integrated approach to the conducting system and its functional vagaries. Knowledge of ion channel functioning under a wide variety of intervention and injury, action potential characteristics in response to such changes, the effects on refractoriness, cell-to-cell communications, and the effects of all of these on conduction patterns is essential if we are to be able to delineate mechanisms for aberrancy with more precision that has been possible to date. There is a large body of experimental data about the cellular electrophysiological properties underlying aberration. A systems approach is needed to make these observations applicable to the human.

1 Lewis T. Paroxysmal tachycardia, the result of ectopic impulse formation. *Heart* 1910;1:262–82.
2 Lewis T. Observations upon disorders of the heart's action. *Heart* 1911/1912;3:279–309.
3 Fisch C. Aberration: seventy five years after Sir Thomas Lewis. *Br Heart J* 1983;40:297–302.
4 Lewis T. Certain physical signs of myocardial involvment. *BMJ* 1913;1:484–9.
5 Shearn HA, Rytand DA. Intermittent bundle branch block. Observations with special reference to the critical heart rate. *Arch Intern Med* 1953;91:448–63.
6 Lewis T. *The mechanism and graphic registration of the heart beat*. 2nd ed. London: Shaw and Sons, 1920:251.
7 Wellens HJJ. Unusual occurrence of nonaberrant conduction in patients with atrial fibrillation and aberrant conduction. *Am Heart J* 1969;77:158–66.
8 Levi RJ, Salerno JA, Nau GJ, Elizari MV, Rosenbaum MB. A reappraisal of supernormal conduction. In: Rosenbaum MB, Elizari MV, eds. *Frontiers of cardiac electrophysiology*. Boston: Martinus Nijhoff, 1983:427–56.
9 Fisch C. *Electrocardiography of arrhythmias*. Philadelphia: Lea & Febiger, 1990:241.
10 Glassman RD, Zipes DP. Site of antegrade and retrograde functional right bundle branch in the intact canine heart. *Circulation* 1981;64:1277–86.
11 Moe GK, Mendez C, Han J. Aberrant A-V impulse propagation in the dog heart: a study of functional bundle branch block. *Circ Res* 1965;16:261–86.
12 Spurrell RAJ, Krikler DM, Sowton E. retrograde invasion of the bundle branches producing aberration of the QRS complex during supraventricular tachycardia studied by programmed electrical stimulation. *Circulation* 1974; 50:487–95.
13 Ashman R, Byer E. Aberration in the conduction of premature ventricular impulses. *J La State Univ Sch Med* 1946;8:62–5.
14 Gouaux JL, Ashman R. Auricular fibrillation with aberration simulating ventricular paroxysmal tachycardia. *Am Heart J* 1947;34:366–73.
15 Nau GJ, Elizari MV, Rosenbaum MB. The different varieties of 2:1 bundle branch block. In: Rosenbaum MB, Elizari MV, eds. *Frontiers of cardiac electrophysiology*. Boston: Martinus Nijhoff, 1983:487–500.
16 Friedberg HD, Schamroth L. The Wenckebach phenomenon in left bundle branch block. *Am J Cardiol* 1969; 24:591–3.
17 Cohen HC, D'Crux I, Arbel ER, Langendorf R, Pick A. Tachycardia and bradycardia-dependent bundle branch block alternans. Clinical observations. *Circulation* 1977;55:242–6.
18 Denes P, Wu D, Dhingra R, Pietras RJ, Rosen KM. The effects of cycle length on cardiac refractory periods in man. *Circulation* 1974;49:32–41.
19 Elizari MV, Nau GJ, Levi RJ, Lazarri JO, Halpern MS, Rosenbaum MB. Experimental production of rate-dependent bundle branch block in the canine heart. *Circ Res* 1974;34:730–42.
20 Dressler W. Transient bundle branch block occurring during slowing of the heart beat and following gagging. *Am Heart J* 1959;58:760–4.
21 Jalife J, Antzelevitch C, Lamanna V, Moe GK. The cellular mechanism of bradycardia-dependent bundle block [abstract]. *Circulation* 1980;62(suppl III):55.
22 Katz A, Pick A. The transseptal conduction time in the human heart. *Circulation* 1963;27:1061–70.
23 Wellens HJJ, Durrer D. Supraventricular tachycardia with left aberrant conduction due to retrograde invasion into the left bundle branch. *Circulation* 1968;38:474–9.
24 Fisch C, Zipes DP, McHenry PL. Rate dependent aberrancy. *Circulation* 1973;48:714–24.
25 Scherf D. Experimentelle und klinische Untersuchungen uber interventrikulare Leitungsstorungen. *Wein Arch Inn Med* 1927;14:443–62.
26 Fisch C. Bundle branch block after ventricular tachycardia: a manifestation of "fatigue" or "overdrive suppression." *J Am Coll Cardiol* 1984;3:1562–4.
27 Izumi K. Direct Wenckebach periods in left bundle branch during bradycardia dependent left bundle branch block in a patient with sick sinus syndrome. *J Cardiol* 1980; 13(3):291–6.
28 Burchell HB. Sino-auricular block, interference dissociation, and different recovery rates of excitation in the bundle branches. *Br Heart J* 1949;11:230–6.
29 Jalife J, Antzelevitch C, Lamanna V, Moe GK. Rate-dependent changes in excitability of depressed cardiac Purkinje fibers as a mechanism of intermittent bundle branch block. *Circulation* 1983;67:912–22.
30 Friedman PL, Wit AL, Hoffman BF. Experimental myocardial infarction: alterations in electrophysiological properties of surviving cells [abstract]. *Bull NY Acad Med* 1972;48:1037.
31 Cranefield PF, Klein HO, Hoffman BF. Conduction of the cardiac impulse. I. Delay, block and one-way block in depressed Purkinje fibers. *Circ Res* 1971;28:199–219.
32 Mendez C, Mueller WF, Merideth J, Moe G. Interaction of transmembrane potentials in canine Purkinje fibers and at Purkinje fiber-muscle junctions. *Circ Res* 1969;24:361–72.
33 Singer DH, Lazzara R, Hoffman BF. Interrelationships between automaticity and conduction in Purkinje fibers. *Circ Res* 1967;21:537–58.
34 Janse MJ, van der Steeen ABM, van Dam RT, Durrer D. Refractory period of dogs ventricular myocardium following sudden changes in frequency. *Circ Res* 1969;24: 251–62.
35 Schuilenburg RM, Durrer D. Rate dependency of functional block in the human His bundle and bundle branch Purkinje system. *Circulation* 1973;48:526–40.
36 Chilson DA, Zipes DP, Heger JJ, Browne KF, Prystowsky EN. Functional bundle branch block: discordant response of right and left bundle branches to changes in heart rate. *Am J Cardiol* 1984;54:313–6.

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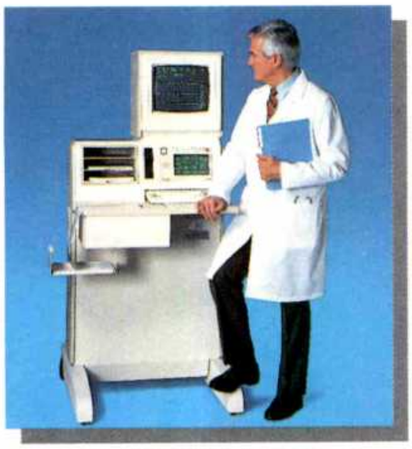

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

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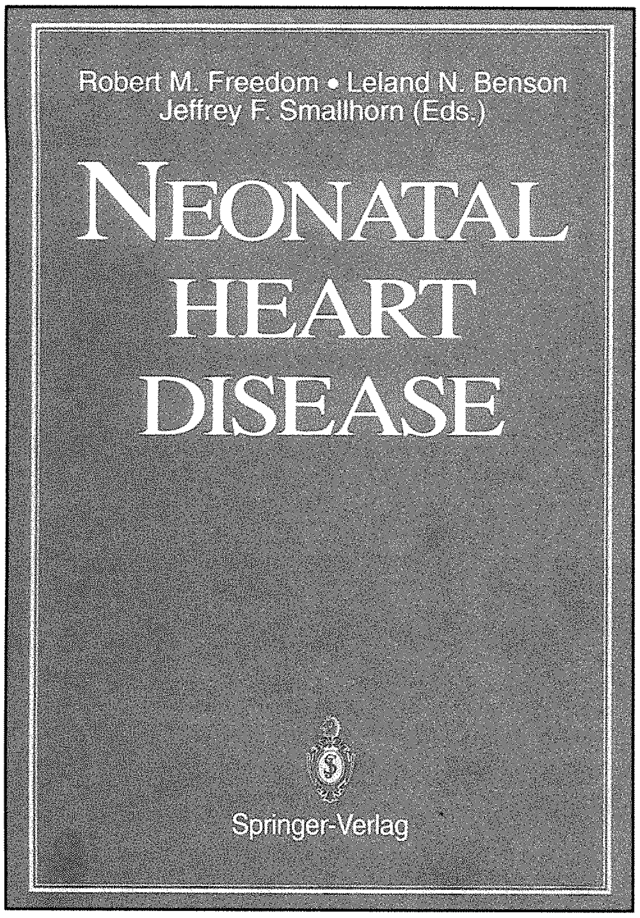

Robert M. Freedom • Leland N. Benson
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Antiarrhythmic drug treatment: need for continuous vigilance

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Abstract
Any physician treating cardiac arrhythmias should be aware of a possible worsening of the arrhythmia (so-called arrhythmogenesis) after the start of antiarrhythmic drug treatment. To facilitate the recognition of that complication the type and possible mechanisms of arrhythmogenesis are reviewed. Recognition also requires an understanding of (a) the time of appearance of arrhythmogenic effects after different drugs, (b) the value of non-invasive and invasive tests, and (c) the profile of the patient most likely to develop this problem. Guidelines are given to reduce the incidence of the arrhythmogenic effects of antiarrhythmic drugs and a plea is made that the physician should be always on the alert for this complication.

Dr Dennis Krikler's expertise in the electrocardiography and electrophysiology of cardiac arrhythmias is well known and admired worldwide. For his festschrift we selected a topic that has interested him for a long time[1 2]: the occurrence of cardiac arrhythmias induced by medication prescribed to treat the arrhythmia.

Many thousands of patients are taking medication because of a cardiac arrhythmia. There is increasing awareness that approximately 15% of patients show worsening of their arrhythmia or the appearance of a new arrhythmia after they have started antiarrhythmic drug treatment. This so-called arrhythmogenic effect or arrhythmogenesis can be life-threatening.[3-7]

The results of the CAST study[8 9] also made the public aware of the possible dangers of antiarrhythmic drug treatment. Physicians treating cardiac arrhythmias need to be familiar with the risk of drug treatment and to be able to recognise it. We suggest a practical approach to the different types of arrhythmogenesis that may develop after antiarrhythmic drug administration and we briefly review the possible types and mechanisms of arrhythmogenesis, which have been discussed extensively elsewhere.[5 10-13] We also discuss the timing of the appearance of arrhythmogenesis after start of antiarrhythmic drug treatment, discuss the value of different non-invasive and invasive tests to document arrhythmogenesis or to recognise patients at an increased risk of developing this problem, and offer guidelines to reduce its incidence.

Types and possible mechanisms of arrhythmogenesis

It is useful to classify the different types of arrhythmogenic effects[5-7] (table 1) because it facilitates their recognition and may help to identify possible mechanisms.

WORSENING OF AN ALREADY MANIFEST ARRHYTHMIA

After antiarrhythmic drug administration the same arrhythmia may occur more frequently, last longer or become less well tolerated because the rate increases. Table 2 shows that this category includes patients with isolated ventricular extrasystoles or non-sustained ventricular tachycardia in whom sustained (fig 1) or even incessant ventricular tachycardia subsequently develops. Patients with atrial flutter and atrial fibrillation in whom drug-induced slowing of the atrial rate results in more atrial impulses being conducted through the atrioventricular node also belong to this category (fig 2).

Facilitation of unidirectional block and of slowing in conduction velocity within the reentry circuit are the most likely mechanisms for drug-induced worsening of an arrhythmia based upon reentry. By slowing intraventricular conduction class Ia and Ic drugs can

Table 1 Classification of the arrhythomogenic effects of antiarrhythmic drugs

(1) Worsening of an already manifest arrhythmia
(2) Induction of block or suppression of escape mechanism(s)
(3) Uncovering of a hidden arrhythmia mechanism
(4) Induction of a new arrhythmia mechanism
(5) Combinations of 1 to 4.

Table 2 Worsening of an already manifest arrhythmia

Mechanism
- Creation of a more stable reentry circuit by shortening of the wavelength and/or widening of the echo zone.
- Decrease in atrial rate of atrial flutter or fibrillation leading to increased impulse conduction through the atrioventricular node.

Type of drugs Ia, Ic, II, IV, digitalis

Examples
- Extrasytoles→nonsustained tachycardia
- Non-sustained tachycardia→sustained tachycardia
- Paroxysmal tachycardia→incessant tachycardia
- Slowing in atrial flutter rate→1 to 1 atrioventricular conduction

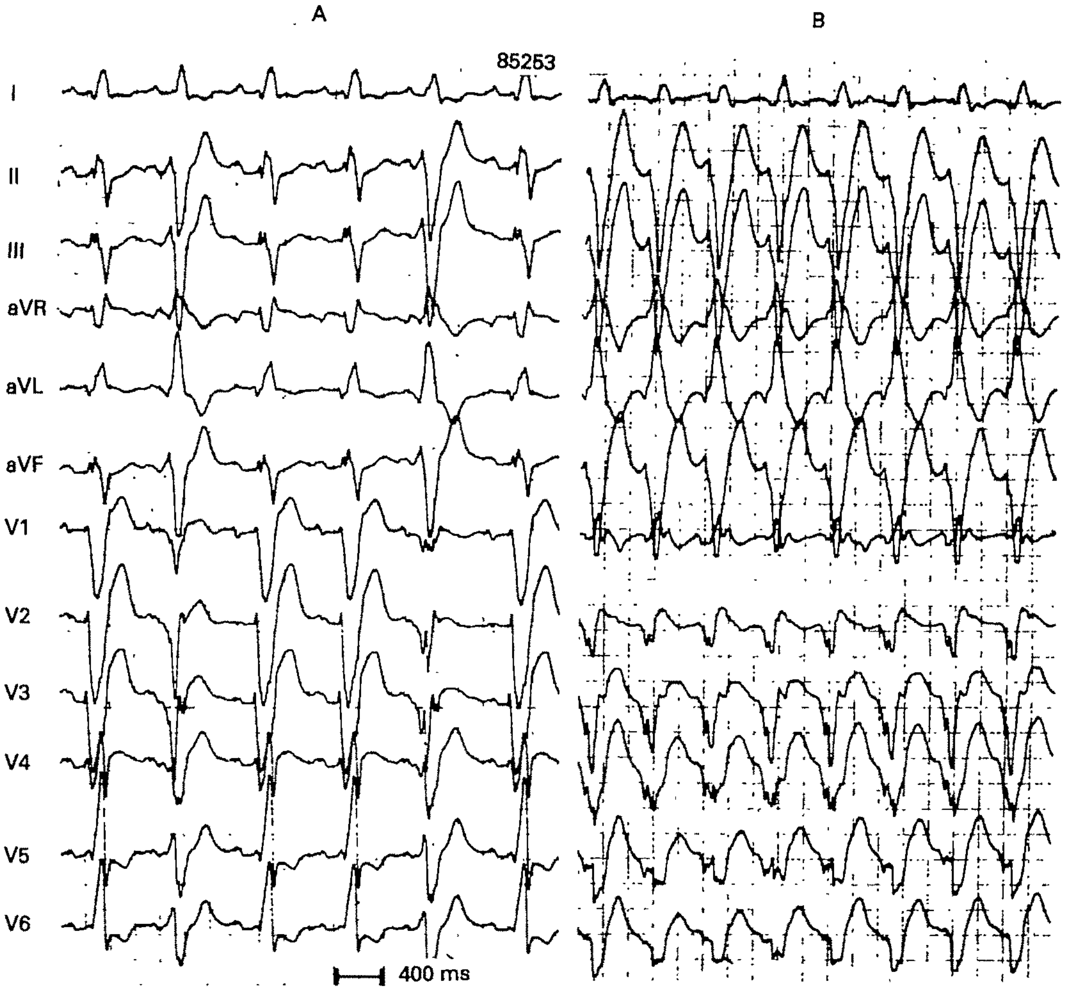


Figure 1 (A) Ventricular extrasystoles in a patient with an old anteroseptal infarction. (B) After treatment with the procainamide he developed sustained uniform ventricular tachycardia with the same QRS confirmation as the isolated ventricular extrasystoles. In A and B the 12 electrocardiographic leads were recorded simultaneously.

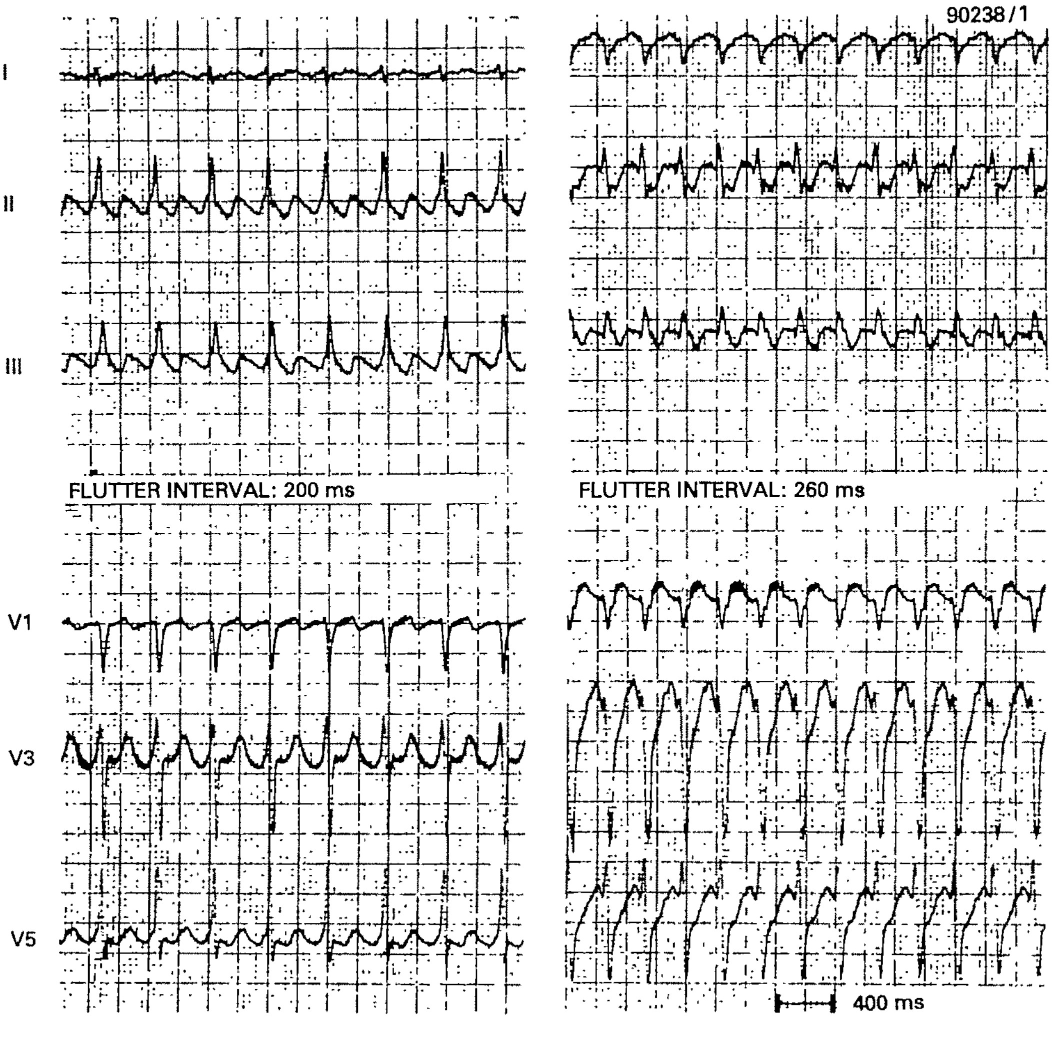
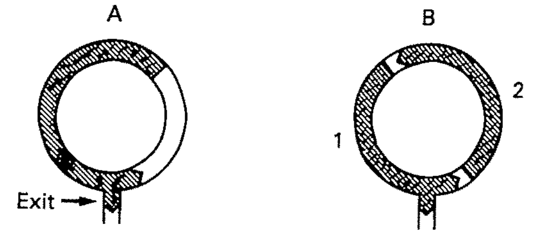


Figure 2 Example of acceleration in ventricular rate after procainamide administration in a patient with atrial flutter. (A) Atrial flutter (flutter interval 200 ms) with 2 to 1 atrioventricular relation resulting in a ventricular rate of 150/min. (B) During procainamide administration slowing in flutter rate (flutter interval 260/ms was followed by 1 to 1 atrioventricular conduction and a ventricular rate of 230/ms.



WL = CV × RP:	10 cm/s × 250 ms = 2·5 cm	7·5 cm/s × 250 ms = 1·88 cm
Circuit length:	4 cm	4 cm
Exit activated:	150/min	2 × 113/min = 226/min

Figure 3 Possible mechanism of acceleration of tachycardia rate by a drug that slows conduction velocity but does not prolong the refractory period. (A) A reentrant circuit with a length of 4 cm and a single exit point. The wavelength (WL) of the circulating impulse (the product of conduction velocity (CV) and the refractory period (RP) measures 10 cm/s × 250 ms = 2·5 cm. Each minute 150 impulses will leave the exit point. (B) After administration of a drug (such as a class Ic drug) that slows conduction without lengthening the refractory period (RP) within the circuit. The wave-length now measures 7·5 cm/s × 250 ms = 1·88 cm. This means that two consecutive impulses can fit within the circuit of 4 cm. Each minute 2 × 113 = 226 impulses will reach the exit point of the circuit. This mechanism of tachycardia acceleration after antiarrhythmic drug administration accords with the results of a recent study.[14]

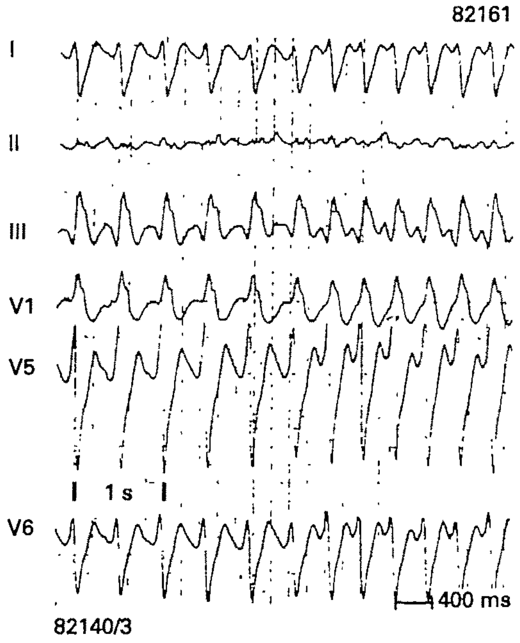


Figure 5 Clinical example of sudden acceleration in rate of a ventricular tachycardia without change in QRS configuration during the intravenous injection of a class Ic antiarrhythmic drug. Possible mechanisms for this type of ventricular tachycardia acceleration include those shown schematically in figs 3 and 4.

facilitate the induction and perpetuation of ventricular arrhythmias. Paradoxically, drugs that slow intraventricular conduction may increase the rate of a tachycardia by using a smaller reentry circuit or by allowing two consecutive impulses within one reentry circuit[14] (figs 3–5). Drugs slowing intra-atrioventricular nodal conduction such as calcium antagonists, β blocking agents, and digitalis may favour the continuation of a reentrant arrhythmia if the atrioventricular node is incorporated in the circuit.

INDUCTION OF A BLOCK OR SUPPRESSION OF ESCAPE MECHANISMS

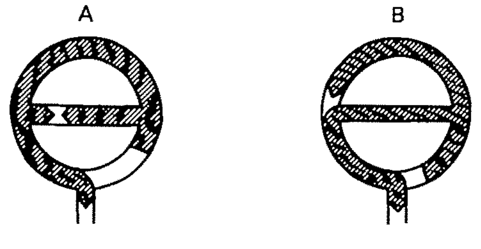
Although the antiarrhythmic drug terminates or suppresses the ectopic rhythm it may worsen the condition of the patient because it also blocks conduction or suppresses escape mechanisms. Drugs can induce bradycardia and even asystole by creating sinus arrest or sinoatrial or atrioventricular block (table 3). Class Ib drugs may suppress atrioventricular junctional or ventricular escape mechanisms.

UNCOVERING A "HIDDEN" ARRHYTHMIA MECHANISM

This category (table 4) includes patients in whom a dormant reentry circuit becomes manifest when an antiarrhythmic agent changes the refractory period and conduction velocity—for example, when a patient with an old myocardial infarction and ventricular extrasystoles develops sustained ventricular tachycardia after the administration of an antiarrhythmic drug (fig 6). This phenomenon can be seen after class Ia and class Ic drugs. These drugs slow myocardial conduction without prolonging the duration of the refractory period. This shortens the wave-length of the circulating impulse allowing it to "fit" within a reentry circuit.

INDUCTION OF A NEW ARRHYTHMIA MECHANISM

An antiarrhythmic drug can induce a new



WL = CV × RP:	10 cm/s × 250 ms = 2·5 cm	7·5 cm/s × 250 ms = 1·88 cm
Circuit length:	4 cm	2 cm
Exit activated:	150/min	225/min

Figure 4 Another possible mechanism of tachycardia acceleration after administration of a drug that slows conduction velocity. Slowing of the conduction velocity means that a smaller reentry circuit can be used and this leads to more impulses leaving the exit point. See legend to fig 3 for abbreviation.

Table 3 Possible site(s) of block in relation to different types of antiarrhythmic agents

	Site of block		
Class	*Sinoatrial*	*Av nodal*	*His-Purkinje*
Ia	+	−	+
Ib	−	−	+
Ic	+	−	+
II	+	+	−
III	+	+	+
IV	−	+	−
Digitalis	+	+	−

Class Ia includes quinidine, procainamide, disopyramide, ajmaline; *class Ib* lignocaine, tocainide, mexiletine, dephenylhydantoin; *class Ic* encainide, flecainide, propafenone; *Class II* β blocking agents; *class III* sotalol, amiodarone; *class IV* verapamil, diltiazem.

Table 4 Uncovering of a hidden arrhythmia mechanism

Mechanism: Creation of a reentry circuit by causing unidirectional block and sufficient slowing in impulse conduction.

Type of drugs: Ia, Ic, III

arrhythmic mechanism (table 5)—for example the induction of early afterdepolarisations by class Ia and class III (sotalol, amiodarone) drugs leading to multiform ventricular tachycardia[11-13 15] (figs 7 and 8) or the induction of ectopic impulse formation based on later afterdepolarisations as in digitalis intoxication.[16]

COMBINATIONS OF DIFFERENT MECHANISMS

Arrhythmogenic effects after drug administration may also occur because of combinations of different mechanisms. Figure 9 shows that administration of a class Ic agent in a patient with the Wolff-Parkinson-White syndrome prevented atrial fibrillation but also allowed the development of incessant circus movement tachycardia, an arrhythmia that had not been clinically present before. In that patient the antiarrhythmic drug prevented atrial fibrillation from occurring and created complete anterograde block in the accessory pathway. Because of persistence of retrograde conduction through the accessory pathway circumstances were created for a circus movement tachycardia with atrioventricular conduction over the atrioventricular node and ventriculoatrial conduction over the accessory pathway. Another example is the patient with atrial fibrillation or atrial flutter who after treatment with a class Ic agent develops a high ventricular rate because a decrease in the number of atrial impulses allows more impulses to pass through the atrioventricular node to the ventricle. This increase in ventricular rate may result in rate dependent slowing in intraventricular conduction (manifest as widening of the QRS complex) and the initiation of serious ventricular arrhythmias.[17] This category includes patients in whom the administration of a class Ia or class III drug leads to the development of bradycardia (for example because of sinoatrial block) and facilitates the emergence of arrhythmias based upon early afterdepolarisations (torsades de pointes).

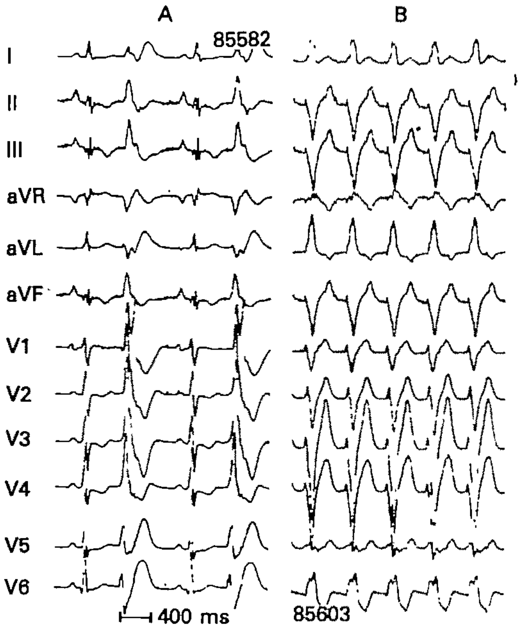


Figure 6 Example of the emergence of sustained uniform ventricular tachycardia after treatment of isolated ventricular extrasystoles (A) with a class Ic agent. Unlike fig 1 the QRS configuration of the ventricular extrasystole is completely different from the one seen during ventricular tachycardia. This suggests that a "dormant" reentry circuit has been exposed by the administration of the antiarrhythmic agent.

Time of appearance of arrhythmogenic effects

The onset of an arrhythmogenic effect after antiarrhythmic drug treatment can vary. Some proarrhythmic effects such as the occurrence of torsades de pointes after class Ia or class III drugs frequently occur early.[18] They are not dose related but based upon an idiosyncratic response to the drug. One dose of quinidine can be sufficient to initiate torsades de pointes[19] (figs 7 and 8). However, as Nguyen *et al* pointed out[20] half of the patients developing arrhythmogenic effects after class Ia drugs do so more than a week after the start of treatment. Arrhythmogenic effects can appear at so-called therapeutic drug concentrations not only because of a drug-induced shortening in wavelength of a circulating impulse resulting in a more stable reentry circuit, but also because of changes in electrolyte concentrations or because of ischaemia in the arrhythmogenic area. Arrhythmogenic effects can also occur when an antiarrhythmic drug reaches a toxic concentration as for example in digitalis intoxication.

Different types of arrhythmogenic effects can be caused by the same drug at different times after the start of its administration. Absence of one type of arrhythmogenesis does not mean that another type of arrhythmogenesis will not occur. A patient who does not develop torsades de pointes after the first dose of quinidine may show a change from a non-sustained to incessant ventricular tachycardia after two weeks of quinidine treatment when a dose favouring a more stable circulation of the impulse within a reentry circuit is reached. The CAST study showed increased arrhythmic events after encainide/flecainide during the whole period of administration of the antiarrhythmic drug.[8 9] Table 6 suggests possible mechanisms for that finding.

Tests to recognise or document increased risk for arrhythmogenesis

RISK PROFILE FOR THE DEVELOPMENT OF ARRHYTHMOGENIC EVENTS

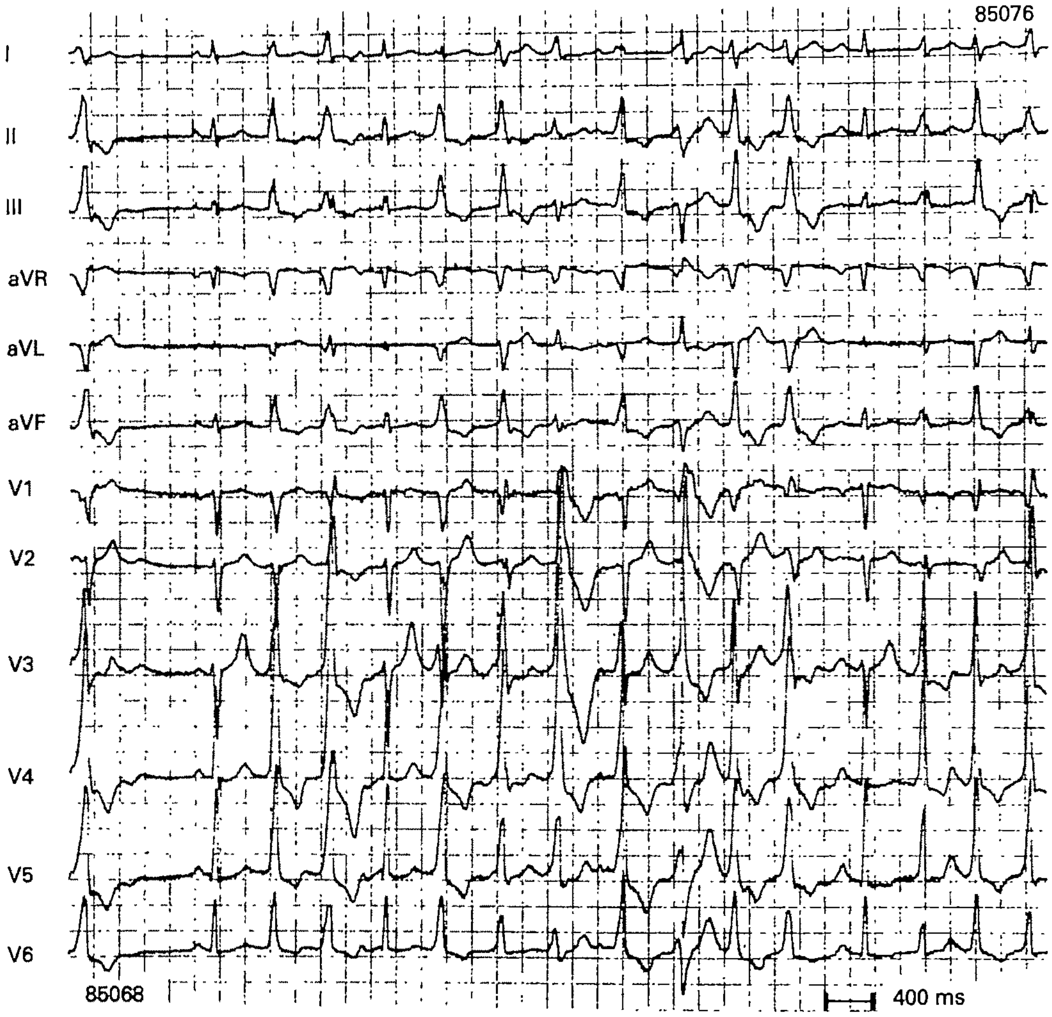
It has repeatedly been stressed that the

Table 5 Induction of a new arrhythmia mechanism

Mechanism
- Early afterdepolarisation (EAD) leading to torsades de pointes
- Delayed afterdepolarisation (DAD) leading to ectopic impulse formation in atrium, atrioventricular junction, and ventricle.

Type of drugs
- EAD: Ia, III
- DAD: digitalis

Figure 7 A simultaneously recorded 12 lead electrocardiogram of a patient with multiform ventricular extrasystoles. The patient, a 24 year old woman had no symptoms and no structural cardiac abnormalities on echocardiography.



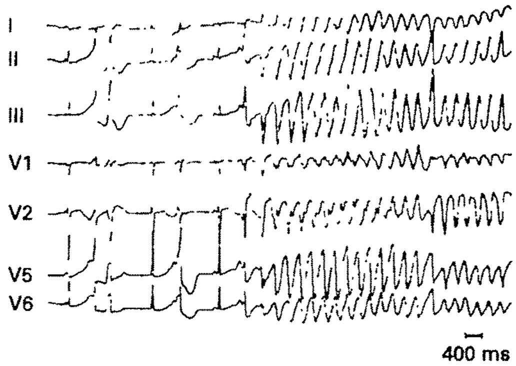
occurrence of an arrhythmogenic effect of an antiarrhythmic drug is unpredictable in individual patients. There are certain characteristics, however, that predispose patients to serious arrhythmogenic events or death during antiarrhythmic treatment. Morgenroth summarised these factors.[22] They include severe structural heart disease, sustained ventricular tachycardia, in-hospital initiation of antiarrhythmic drug treatment, and large doses of antiarrhythmic drugs. Not surprisingly, the sicker the patient the higher the chance of an arrhythmia becoming worse after the start of antiarrhythmic drug treatment.

TWENTY FOUR HOUR ELECTROCARDIOGRAPHIC RECORDING

An arrhythmogenic effect may become manifest shortly after the start of treatment with an antiarrhythmic drug. Examples are the torsades de pointes type of multiform ventricular tachycardia after class Ia or class III drugs and the emergence of sustained uniform ventricular tachycardia in the patient with isolated ventricular extrasystoles or non-sustained ventricular tachycardia after the administration of class Ic drugs.

These changes can be documented by long-term electrocardiographic recording in the first days after the start of antiarrhythmic drug treatment, but as discussed previously, arrhythmogenic changes may also occur even later, so there are practical problems in using long-term electrocardiographic recording to recognise arrhythmogenic effects.

Figure 8 Electrocardiogram from same patient as fig 7 after 200 mg of quinidine sulphate. Note QT prolongation and the emergence of a torsades de pointes type of ventricular tachycardia.



EXERCISE TESTING

Velebit *et al* emphasised the importance of exercise testing in evaluating the possible arrhythmogenic effects of antiarrhythmic agents.[3] Antiarrhythmic drugs can induce rate related slowing of intramyocardial conduction (so-called use-dependent slowing). This can cause widening of the QRS complex with increasing heart rate. Recently, Ranger *et al* showed that some patients treated with flecainide develop considerable widening of their QRS complex followed by the emergence of ventricular tachycardia when they increase their heart rate by exercise.[23] Figure 10 gives an

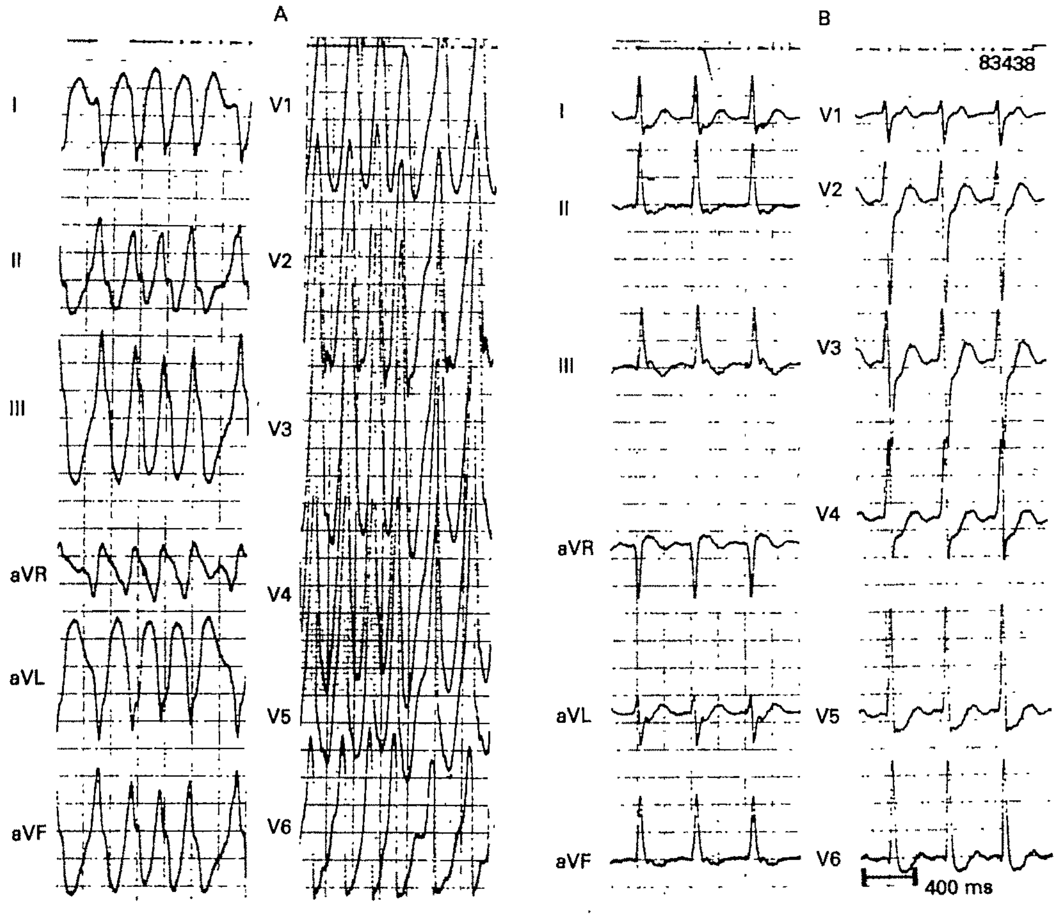


Figure 9 (A) Atrial fibrillation in a patient with a left free wall accessory pathway. This patient had paroxysmal episodes of atrial fibrillation. Administration of a class Ic drug produced anterograde block in the accessory pathway thereby protecting the patient against high ventricular rates during atrial fibrillation. The antiarrhythmic drug did not affect retrograde conduction over the accessory pathway, however, and the patient developed incessant circus movement tachycardia with atrioventricular conduction over the atrioventricular node and ventriculoatrial conduction over the accessory pathway.

example of this phenomenon in a patient who was treated with a class Ic agent because of a non-sustained ventricular tachycardia. During administration of the antiarrhythmic drug the patient noticed that a sustained tachycardia always developed when he exercised. Figure 10 shows that during exercise testing the QRS complex and axis deviation increased considerably and was followed by sustained ventricular tachycardia. Exercise related ventricular tachycardia no longer occurred in this patient when the class Ic agent was replaced by a class III drug.

During exercise testing off drugs Kadish *et al.*[24] found a paradoxical increase in the corrected QT interval in patients who had arrhythmogenic effects on a type Ia drug. Antiarrhythmic drugs may not only produce use-dependent slowing in conduction but also use-dependent prolongation of the refractory period. Figures 11 and 12 show that in a patient with right bundle branch block and left anterior hemiblock a rate-related (use-dependent) block was seen in the left posterior fascicle after flecainide administration. The observations of Ranger *et al*[23] and Kadish and coworkers[24] indicate the need for prospective studies before and during antiarrhythmic drug administration to establish the role of exercise testing in the risk estimation of arrhythmogenesis.

Table 6 Possible mechanisms of deleterious effects of class Ic agents after myocardial infarction

(*a*) Negative inotropic effects.
(*b*) Rate related slowing of intramyocardial conduction favouring initiation of ventricular tachycardia on exercise or after onset of atrial flutter or atrial fibrillation.
(*c*) Slowing in intramyocardial conduction during ischaemia favouring initiation of ventricular tachycardia.[21]
(*d*) Induction of slow heart rates because of sinoatrial or subnodal block.
(*e*) Acceleration of ventricular tachycardia because slowing in intramyocardial conduction may allow two circulating impulses within one reentry circuit or the use of a smaller reentry circuit.

PROGRAMMED STIMULATION OF THE HEART

Several groups of investigators reported on the use of programmed stimulation of the heart to identify the arrhythmogenic effects of antiarrhythmic drugs.[25-28] Induction of a sustained tachycardia in a patient in whom before drug administration only a non-sustained tachycardia could be induced, the initiation of a faster tachycardia by fewer premature beats, and the emergence of incessant tachycardia after antiarrhythmic drug administration have all been regarded as signs of the arrhythmogenic effects of antiarrhythmic agents. The lack of information on the effect of long-term oral drug administration in patients showing the arrhythmogenic "effects" of that drug during programmned electrical stimulation, made us reluctant to regard the development of the arrhythmogenic effects during programmed stimulation as a contraindication to the chronic oral use of such drugs. Also because Ross *et al* reported considerable variation in the number of premature stimuli required to induce sustained ventricular tachycardia on different days[29] we decided to continue antiarrhythmic drug treatment irrespective of the findings

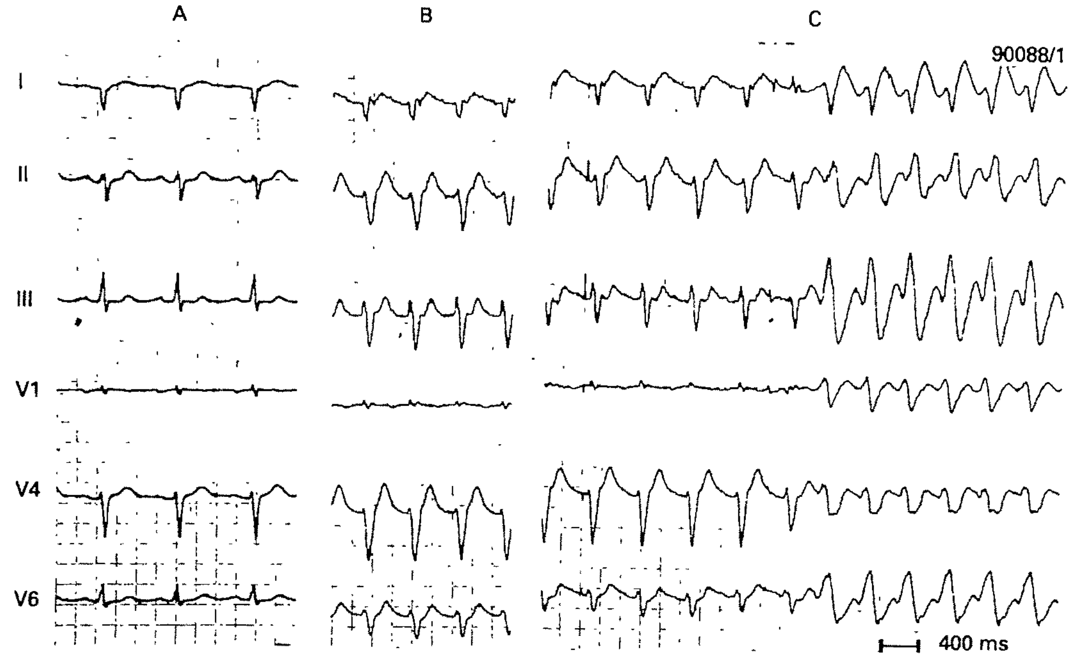


Figure 10 Initiation of sustained ventricular tachycardia during exercise testing in a patient treated with class Ic agent. (A) Electrocardiogram before exercise. The heart rate was 80 beats/min and the QRS width measured 100 ms. (B) During exercise the heart rate was 130 beats/min with a QRS width of 160 ms and left axis deviation. Shortly thereafter (C) a ventricular tachycardia started with a rate of 150 beats/min.

obtained during the programmed stimulation study. No attention was given to the induction of a sustained ventricular tachycardia during drug treatment, when before the drug only a non-sustained arrhythmia could be initiated. The drug was also continued despite induction of a faster tachycardia or induction by fewer premature stimuli. During follow up there were no differences in the occurrence of spontaneous sustained ventricular arrhythmias or of sudden death between patients with or without easier induction or change from induction of a non-sustained to a sustained ventricular tachycardia after antiarrhythmic drug administration.[30] We think that only the induction of an incessant tachycardia after antiarrhythmic drug administration can be accepted as definite evidence of an arrhythmogenic effect of the drug.

The practical approach

Antiarrhythmic drug treatment should be started only when it is clearly indicated by symptoms and/or an arrhythmia with a bad prognosis.[31] The rules outlined in table 7 should be followed to minimise the arrhythmogenic effects and to aid their early recognition. In view of the considerable pharmacokinetic and pharmacodynamic differences between antiarrhythmic drugs we believe that physicians treating cardiac antiarrhythmias should familiarise themselves with selected antiarrhythmic agents and known how these drugs are metabolised and excreted and how they are affected by other medication given concomitantly. In patients with structural heart disease antiarrhythmic drug treatment should be started in hospital, preferably under continuous electrocardiographic monitoring. Exercise testing should be

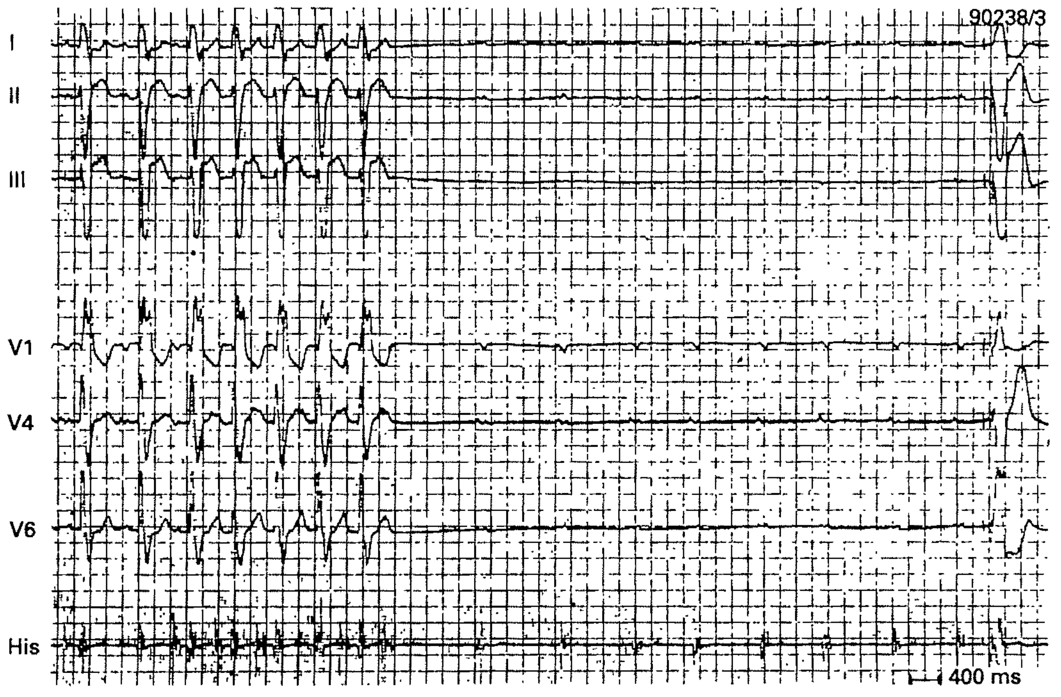


Figure 11 Example of use-dependent prolongation of the refractory period. The recording is from a patient with paroxysmal atrial tachycardia who developed episodes of syncope after being treated with flecainide. Note that atrioventricular conduction goes over the left posterior fascicle. During flecainide administration complete atrioventricular block occurred shortly after a few beats of atrial tachycardia. The trace was made after a pacing wire was inserted. Asystole was terminated by a paced ventricular complex.

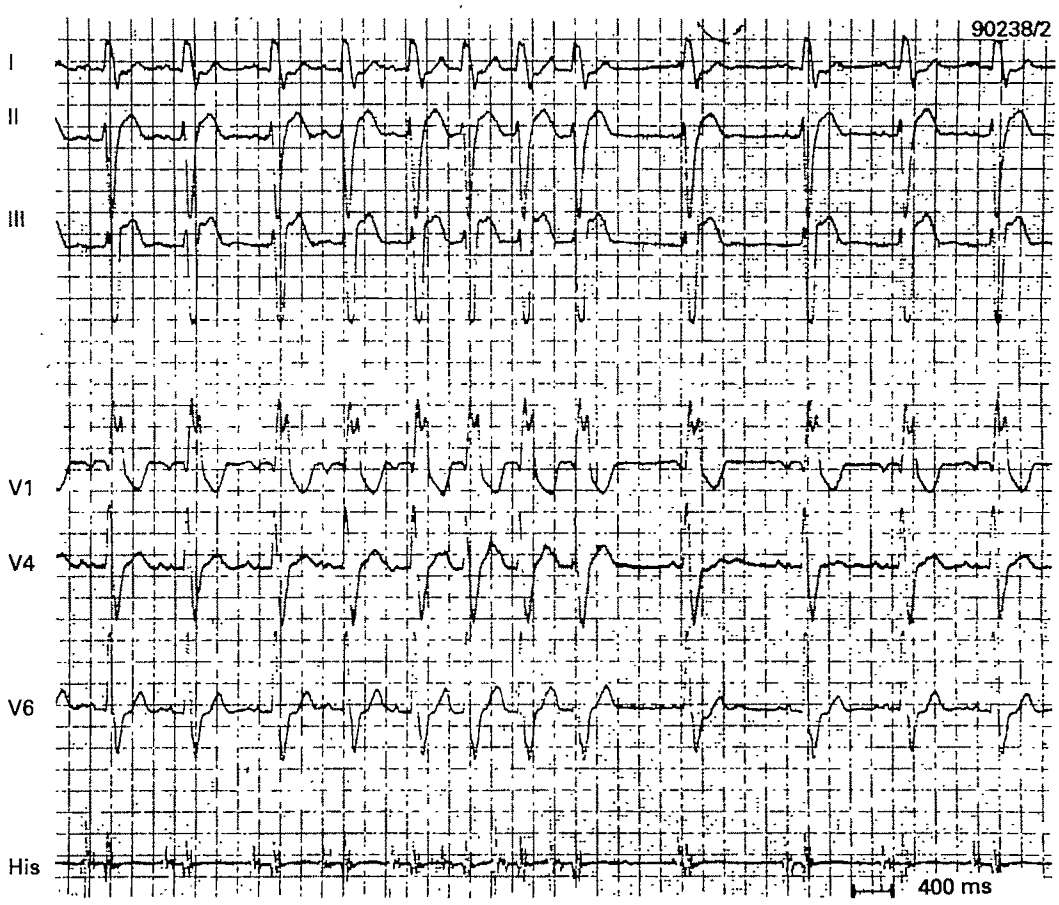


Figure 12 Electrocardiogram from the same patient as figure 11 after flecainide treatment was stopped. Note that rate acceleration during atrial tachycardia is no longer followed by complete atrioventricular block. Figures 11 and 12 suggest that flecainide induced rate-related (use-dependent) prolongation of the refractory period of the left posterior fascicle was responsible for complete atrioventricular block.

performed before and during antiarrhythmic drug administration. The patient should be instructed about the signs and symptoms of worsening of the existing arrhythmia or the appearance of a new one.

Conclusions

Antiarrhythmic agents commonly, have arrhythmogenic effects that are life-threatening and these can occur as long as the patient is taking antiarrhythmic medication. Although, as outlined, certain measures can be taken to minimise the chance of arrhythmogenic effects, the patient and the physician should constantly be alert to this possibility.

Table 7 Measures to minimise arrhythmogenic effects of antiarrhythmic drugs

(*a*) Be certain that the patient needs antiarrhythmic drug treatment.
(*b*) Identify and correct cardiac ischaemia and pump function abnormalities.
(*c*) Correct electrolyte abnormalities.
(*d*) Use an antiarrhythmic drug you know well.
(*e*) Start treatment in hospital while monitoring the ECG if the patient has structural heart disease.
(*f*) Perform exercise testing before and during drug administration.
(*g*) Instruct the patients about signs and symptoms of worsening of existing or appearance of new arrhythmias.
(*h*) Regularly check the function of the organs responsible for breakdown and excretion of the antiarrhythmic drug.
(*i*) Know the possible effects of additional medication on the concentration of the antiarrhythmic drug.

1 Krikler DM. A fresh look at cardiac arrhythmias. *Lancet* 1974;1:913–7.
2 Krikler DM, Curry PVL. Torsade de pointes, an atypical ventricular tachycardia. *Br Heart J* 1976;38:117–20.
3 Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* 1982;65:886–94.
4 Ruskin JN, McGovern MB, Garan H, DiMarco JP, Kelly E. Antiarrhythmic drugs: a possible cause of out-of-hospital cardiac arrest. *N Engl J Med* 1983;309:1302–6.
5 Rosen MR, Wit AL. Arrhythmogenic actions of antiarrhythmic drugs. *Am J Cardiol* 1987;59:10E–8E.
6 Bigger JT, Sahar DJ. Clinical types of proarrhythmic response to antiarrhythmic drugs. *Am J Cardiol* 1987;59:2E–9E.
7 Brugada P, Wellens HJJ. Arrhythmogenesis of antiarrhythmic drugs. *Am J Cardiol* 1988;61:1108–11.
8 The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.
9 Echt DS, *et al.* Mortality and morbidity of patients receiving encainide flecainide or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781–8.
10 Woosley RL, Roden DM. Pharmacologic causes of arrhythmogenic actions of antiarrhythmic drugs. *Am J Cardiol* 1987;59:19E–25E.
11 Cranefield PD, Aronson RS. *Cardiac arrhythmias: the role of triggered activity and other mechanisms.* Mount Kisco: Futura, 1988.
12 Zipes DP. Cardiac electrophysiology: promises and contributions. *J Am Coll Cardiol* 1989;13:1329–52.
13 Jackman WM, Szabo B, Friday KJ, *et al.* Ventricular tachyarrhythmias related to early afterdepolarisations and triggered firing: relationship to QT interval prolongation and potential therapeutic role for calcium channel blocking agents. *J Cardiovasc Electrophysiology* 1990;1:170–95.
14 Brugada J, Boersma L, Kirchoff C, *et al.* Double-wave reentry as a mechanism of acceleration of ventricular tachycardia. *Circulation* 1990;81:1633–43.
15 Jackman WM, Friday KJ, Clark M, *et al.* The long QT syndromes: A critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31:115–72.
16 Gorgels APM, Beekman HDM, Brugada P, Dassen WRM, Richards DAB, Wellens HJJ. Extrastimulus-related shor-

tening of the first post-pacing interval in digitalis-induced ventricular tachycardia: observations during programmed electrical stimulation in the conscious dog. *J Am Coll Cardiol* 1983;1:840–57.

17 Crijns HJ, Van Gelderen JC, Lie KI. Supraventricular tachycardia mimicking ventricular tachcycardia during flecainide treatment. *Am J Cardiol* 1988;62:1303–6.

18 Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med* 1988;319:257–62.

19 Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implication for patient care. *Am Heart J* 1986;111: 1088–93.

20 Nguyen PT, Scheinman MM, Segar J. Polymorphic ventricular tachycardia: clinical characteristics, therapy and the QT interval. *Circulation* 1986;74:340–9.

21 Nattel S, Pedersen DH, Zipes DP. Alterations in regional myocardial distribution and arrhythmogenic effects of aprinidine produced by coronary artery occlusions in the dog. *Cardiovasc Res* 1981;15:80–5.

22 Morgenroth J. Risk factors for the development of proarrhythmic events. *Am J Cardiol* 1987;59:32E–7E.

23 Ranger S, Talajic M, Lemery R, Roy D, Nattel S. Amplification of flecainide-induced ventricular conduction slowing by exercise: a potentially significant clinical consequence of use-dependent sodium channel blockade. *Circulation* 1989;79:1000–6.

24 Kadish AH, Weisman HF, Veltri EP, Epstein AE, Slepian MJ, Levine JH. Paradoxical effects of exercise on the QT interval in patients with polymorphic ventricular tachycardia receiving type Ia antiarrhythmic agents. *Circulation* 1990;81:14–9.

25 Rinkenberger RL, Prystowsky EN, Jackman WM, Naccarelli GV, Heger JJ, Zipes DP. Drug conversion of nonsustained ventricular tachycardia to sustained ventricular tachycardia during serial electrophysiologic studies: Identification of drugs that exacerbate tachycardia and potential mechanisms. *Am Heart J* 1982;103:177–84.

26 Poser RF, Podrid PJ, Lombardi F, Lown B. Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. *Am Heart J* 1985;110:9–16.

27 Au PK, Bhandari AK, Bream R, Schreck D, Siddiqi R, Rahimtoola SH. Proarrhythmic effects of antiarrhythmic drugs during programmed ventricular stimulation in patients without ventricular tachycardia. *J Am Coll Cardiol* 1987;9:389–97.

28 Horowitz LN, Greenspan AM, Rae AP, Kay HR, Spielman SR. Proarrhythmic responses during electrophysiologic testing. *Am J Cardiol* 1987;59:45E–8E.

29 Ross DL, Cooper MJ, Ho B, *et al* Day-to-day reproducibility of ventricular tachycardia induction at electrophysiologic study. *Circulation* 1984;70:399–412.

30 Brugada P, Lemery R, Talajic M, Della Bella P, Wellens HJJ. Treatment of patients with ventricular tachycardia or ventricular fibrillation. In: Brugada P, Wellens HJJ, eds. *Cardiac arrhythmias. Where to go from here?* Mount Kisco: Futura, 1987:457–70.

31 Wellens HJJ, Brugada P. Treatment of cardiac arrhythmias: when, how and where? *J Am Coll Cardiol* 1989;14: 1417–28.

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REVIEW

Progress in familial hypertrophic cardiomyopathy: molecular genetic analyses in the original family studied by Teare

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In this journal in 1958 Donald Teare reported the pathological findings in a series of eight unrelated young adults who died suddenly and who at necropsy had manifested gross asymmetrical hypertrophy of the heart.[1] In a footnote, he noted the recent sudden death of the brother of one of the original cases, thus identifying the familial nature of this condition. The subsequent report[2] of two generations of the family of these two siblings showed that asymmetrical hypertrophy was inherited in a manner consistent with an autosomal dominant trait. The term "obstructive cardiomyopathy" was proposed for these and similar cases, identifying this as a heart muscle disorder. The description of this family initiated the detailed characterisation of this novel syndrome, which was later called familial hypertrophic cardiomyopathy.

Demonstration of a mendelian form of inheritance implied that familial hypertrophic cardiomyopathy was the result of a single gene disorder. Despite 30 years of investigation, however, the pathogenesis of this condition is only now being revealed. Molecular biological techniques were used to identify first the location[3] and later the identity[4,5] of genetic defects responsible for familial hypertrophic cardiomyopathy. The identification of mutations in the cardiac myosin heavy chain (MHC) genes has made familial hypertrophic cardiomyopathy the first primary cardiac disorder to be characterised at the molecular level. An abnormality of the β myosin heavy chain gene is also responsible for disease in the original family described by Teare; we discuss here the benefits of such a genetic diagnosis.

Background

The clinical genetics of familial hypertrophic cardiomyopathy were established by the observation of inheritance patterns in families such as the one described here. Since the advent of cross sectional echocardiography it has been clear that, where the familial condition is familial, it is inherited as an autosomal dominant trait. In a significant minority of cases, hypertrophic cardiomyopathy occurs as an apparently sporadic condition.[6,7] Cases of sporadic disease are defined as those where no first degree relatives are known to be affected. The frequency of such cases will tend to be overestimated by failure to identify subtle forms of the condition in relatives, especially children, of the proband. In many families expression of the disease gene is such that penetrance is virtually complete in adults. This is usually not the case in children, however, where the phenotype frequently does not become manifest until adolescence,[8] or in some families where subclinical disease is present. Until a definitive genetic diagnosis is available the full range of the disease phenotype and the extent and nature of sporadic disease will remain uncertain.

Recent advances in molecular biology have led to the identification of the gene defects responsible for several important inherited conditions, even where there was no prior knowledge of any defect at the protein level (reviewed in reference[9]). In the absence of any apparent candidate genes or of any known cytogenetic abnormality in familial hypertrophic cardiomyopathy, the approach that was adopted was the use of linkage analysis. Linkage analysis depends upon the demonstration of "co-segregation" of a disease trait with a DNA polymorphism of known chromosomal location. If a DNA polymorphism is situated close to the disease gene on a given chromosome, then the presence of the polymorphism at this site will tend to be inherited with the disease trait in a family pedigree. Where a polymorphism and a disease gene are separated by some distance they will tend to become separated by crossovers, or recombinations, during meiois. Thus the extent of co-inheritance, or co-segregation, within a pedigree defines the closeness of linkage. Linkage analyses were performed in a large French Canadian family with familial hypertrophic cardiomyopathy to test systematically a panel of probes that identify polymorphic loci on all chromosomes, until one was found that identified a locus that co-segregated with disease. This search revealed that the gene for familial hypertrophic cardiomyopathy in this family was on chromosome 14, in the region of the genes for the cardiac myosin heavy chains (α and β cardiac MHC genes).[3,10]

Myosin heavy chains are the major structural component of heart muscle, and so were clearly potential candidates for involvement in this disease. The demonstration of a major gene rearrangement affecting the α and β MHC genes in one family[4] led to the hypothesis that the MHC genes were indeed the site of mutations causing disease in familial hypertrophic cardiomyopathy. No such rearrangement was found in the original French Canadian family,

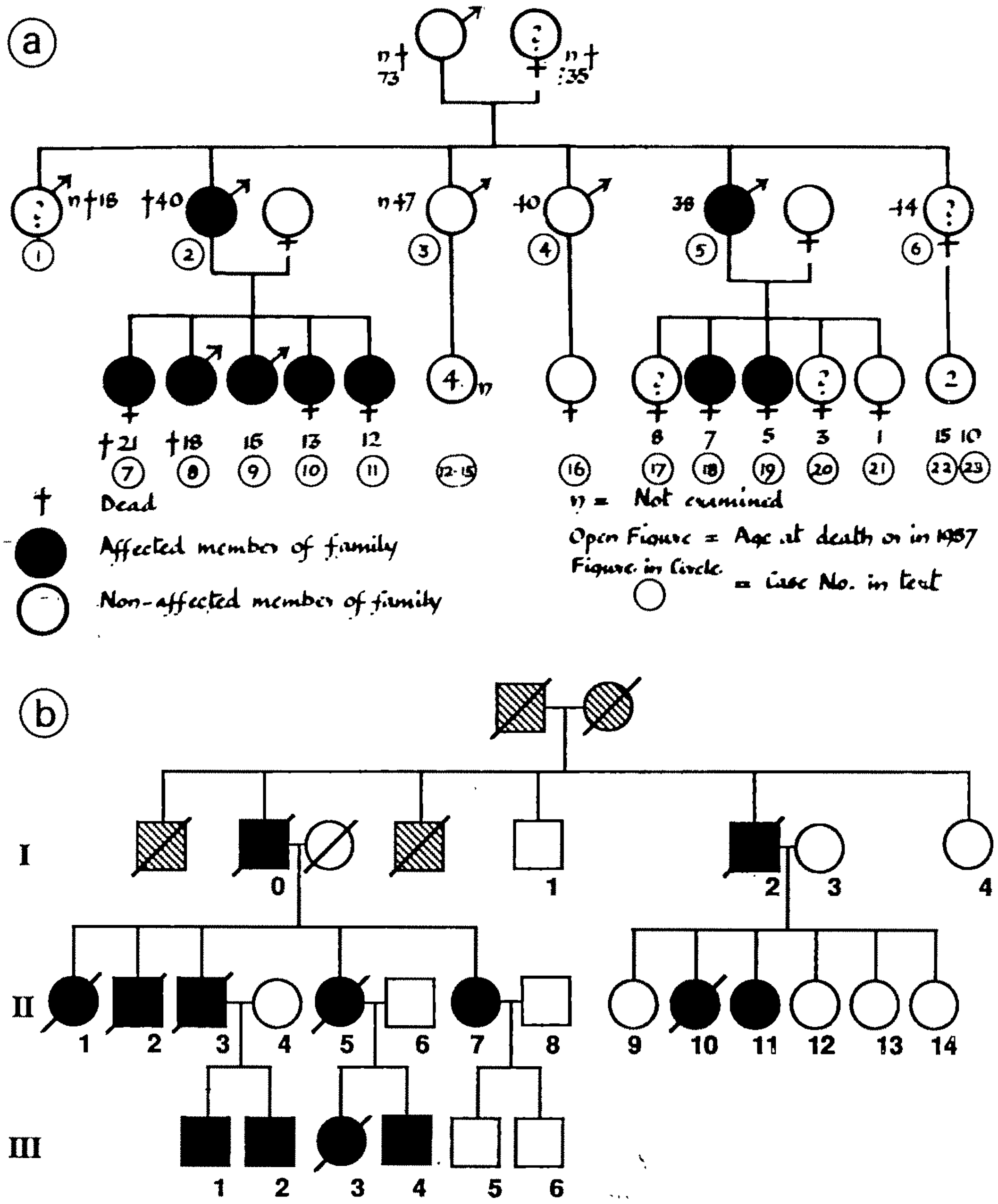

Figure 1 Family pedigree. (a) Original pedigree as depicted by Hollman, Goodwin, Teare, and Renwick.[2] (b) Current pedigree showing the subject number and disease status of family members. Squares are male family members and circles female. Solid symbols are those with hypertrophic cardiomyopathy, open symbols are those unaffected and hatched symbols are those not examined. Those who have died are indicated by an oblique stroke. Members of generations I and II were those described in the original account of this family, with individuals II-1 and II-2 being the presenting cases. Since the 1960 report four of the six surviving affected members have died; one of the two remaining survivors is undergoing transplant assessment. Of the four affected members of generation III one has died and one has been resuscitated from an out of hospital cardiac arrest.

thus necessitating a detailed search for a point mutation. Each of the MHC genes contains approximately 30 000 nucleotides, making identification of a single base pair substitution very difficult. Such a mutation, however, was identified in exon 13 of the β cardiac MHC gene in this family, that results in the conversion of a highly conserved arginine residue to a glutamine residue.[5]

These findings have generated several further questions. In particular, linkage data have shown that not all familial hypertrophic cardiomyopathy can be attributed to MHC mutations on chromosome 14.[11] However, conventional linkage analyses are frequently uninformative in smaller families and so have not detailed the proportion of familial hypertrophic cardiomyopathy that results from myosin mutations. Also, the two described mutations implicate different mechanisms for the pathogenesis of the autosomal dominant phenotype. Studies were therefore undertaken to document the presence of myosin mutations in other families with familial hypertrophic cardiomyopathy. As in the French Canadian family, no major rearrangements or deletions were found in the MHC genes of 40 unrelated families with familial hypertrophic cardiomyopathy, suggesting that point mutations were likely to be the predominant mutations causing disease (Tanigawa *et al.* Unpublished). This finding led to the development of a screening technique for analysing the protein coding section of the β MHC gene for sequence abnormalities. Such polymorphisms can be used to detect linkage to the MHC locus and, if they are linked they are excellent candidates for being disease-causing mutations. The success of this technique is illustrated by its application to the original Teare family.

Clinical evaluation

Not surprisingly the family with familial hypertrophic cardiomyopathy that first came to medical attention was one with particularly

Clinical findings in affected family members

Pedigree number	*Age at D/FU*	*Chest pain*	*Dyspnoea (NYHA)*	*Syncope*	*Abnormal ECG*	*AF/emboli*	*LVH*	*RVH*	*LVOT gradient*	*Clinical events*
I–0	40/M	+	III	–	+	–	530 g	+	–	Sudden death
I–2	52/M	+	II	+	+	–	–	–	–	Sudden death
II–1	21/F	+	III	–	+	–	450 g	+	+	Sudden death
II–2	18/M	–	I	+	–	–	425 g	–	–	Sudden death
II–3	42/M	+	III	+	+	+	–	+	+	Died awaiting transplant
II–5	32/F	–	III	+	+	–	–	–	–	Died CHF
II–7	45/F	–	III	–	+	–	17 mm	–	–	Transplant assessment
II–10	20/F	–	II	+	+	–	490 g	+	+	Sudden death
II–11	39/F	–	II	–	+	–	13 mm	+	–	Alive
III–1	24/M	–	I	–	+	+	14 mm	+	+	AF→circulatory collapse
III–2	22/M	–	I	+	+	–	13 mm	–	+	Out of hospital VF
III–3	23/F	+	III	+	+	+	20 mm	–	+	Died after myomectomy
III–4	22/M	+	II	–	+	–	25 mm	+	+	Alive

AF, atrial fibrillation; Age at D/FU, age at death or current follow up; CHF, congestive heart failure; LVH, left ventricular hypertrophy cited as cardiac weight at necropsy or maximum LV wall thickness on echocardiography; LVOT gradient, LV outflow tract gradient at catheterisation or the presence of systolic anterior motion of the mitral valve on echocardiography; RVF, right ventricular hypertrophy; VF, ventricular fibrillation.

severe disease, enabling Hollman *et al* to make a remarkably complete account of the range of symptoms, signs, findings on investigation, and complications of this condition.[2] Thus the high incidence of sudden death, progressive heart failure, and cerebral embolus was identified. The presence of "extensive scattered fibrosis" was described and considered to be a possible anatomical basis for ventricular fibrillation. Hollman *et al* noted that the unifying pathological features were more consistent within this condition than the clinical features were within the one family.

Thirty-two years of follow up data are now available on this family (fig 1, table 1). While there is a range of disease severity, this is a family with an especially malignant natural history. Of 13 affected individuals six died suddenly or experienced an out of hospital cardiac arrest. Another has been successfully resuscitated from acute circulatory collapse associated with the onset of atrial fibrillation. Six of these seven individuals were symptom-free before their premature sudden cardiac death, which occurred at ages between 18 and 52 years. Those who have died suddenly had mild to moderate myocardial hypertrophy but considerable myocyte and myofibrillar disarray with extensive myocardial fibrosis.

Faced with such a severe disease there was a move to undertake myomectomy, partly in an attempt to modify prognosis, in addition to controlling symptoms attributable to obstruction of the left ventricular outflow tract. Two of those who underwent myomectomy (II-3 II-5) died in congestive heart failure shortly afterwards (one while awaiting transplantation) while the third patient died (III-3) in a high output state within hours of operation for severe mitral regurgitation and left ventricular outflow obstruction. This individual had been on long term amiodarone treatment before operation for paroxysmal atrial fibrillation associated with generalised seizures.

Molecular studies

The molecular genetic techniques devised to screen for β MHC mutations have been described in detail elsewhere.[12] In brief, segments of DNA from the β cardiac MHC genes of an affected individual are amplified in vitro by the polymerase chain reaction. These products are analysed in an RNase protection assay which identifies mismatches between patient DNA and a normal control sequence. The entire coding sequence (approximately 6000 base pairs) can be examined, in sections of up to 500 base pairs at a time. DNA extracted from peripheral leucocytes of individual III-2 was

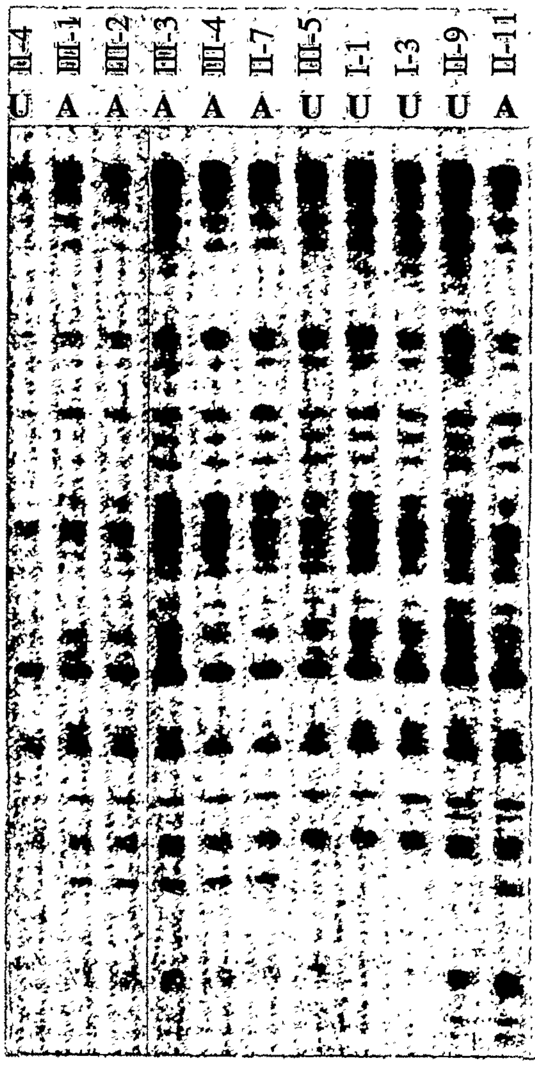

Figure 2 Detection of a sequence mismatch in exon 14 in affected family members. An RNase protection assay of exon 14 is shown. DNA samples from unaffected (U) and affected (A) individuals are identified by pedigree number. The assay showed an abnormal fragment (arrowed) that was present only in affected individuals. This fragment indicates cleavage of the normal RNA probe sequence because of a sequence mismatch with the DNA from affected individuals.

screened in this way. The analysis showed evidence of a sequence mismatch in exon 14 in this individual. A similar analysis of the remaining family members showed this abnormality in all affected members (fig 2). In contrast, this mismatch was not present in unaffected family members. The association of this abnormality in myosin with the disease shows linkage of the familial hypertrophic cardiomyopathy trait to the MHC locus in this family, with a LOD score (logarithm of the odds) of 3·9 (odds of almost 10 000 to 1 in favour of linkage).

This abnormality in exon 14, which shows complete concordance with disease status throughout the family and which to date has not been seen in unaffected individuals, is the likely candidate for being the disease-causing mutation. Further characterisation of this defect will establish the precise abnormality in MHC gene and its polypeptide structure.

Implications of genetic diagnosis

The detection of an abnormality within the β myosin heavy chain gene in a family such as this makes the subsequent diagnosis of disease state very simple in any family member. The diagnosis can be made definitively in children and adolescents in these families and also in those adults who are difficult to diagnose clinically.[12] Similarly, unaffected individuals can be told with certainty that they and their offspring will remain free of the condition, thereby avoiding the need for serial clinical screening. Although the surviving members of this family all have had correctly assigned clinical diagnoses it is noteworthy that sudden death has been the presenting feature in this family in the past. As members of generation III approach reproductive age it is now possible to screen their offspring and establish the diagnosis at any stage.

A genetic diagnosis made preclinically or even prenatally identifies individuals at risk of the complications of familial hypertrophic cardiomyopathy before the development of clinically detectable abnormalities. For the first time, it is now possible to study the natural history before established hypertrophy or complications of familial hypertrophy cardiomyopathy develop. This means that treatment can be started early and its effects on the disease process or its consequences can be studied longitudinally. In particular, individuals identified in this way as having familial hypertrophic cardiomyopathy can be assessed for risk factors for sudden death to allow for appropriate interventions. It is hoped that early diagnosis and use of existing treatment will already be sufficient to reduce the burden of the disease in families such as the one described here. Perhaps more importantly, the opportunity to perform prospective trials of intervention early in the course of familial hypertrophic cardiomyopathy should generate even more effective treatment in the future.

It is also expected that knowledge of the genetic basis of familial hypertrophic cardiomyopathy in a family or an individual may provide more than a means of definitive diagnosis—by also providing a prognostic indicator. There is considerable variability in the severity of familial hypertrophic cardiomyopathy among different families, with some (such as the family Teare studied) showing far greater morbidity and mortality than others.[13–15] Despite the acknowledged variability of expression within a given family,[16] such trends that characterise a particular family are most likely to result from the influence of the specific disease-causing mutation. As more disease-causing mutations are identified, a genetic classification is becoming available for some familial hypertrophic cardiomyopathy families, so that it is now possible to begin determining the influence of the type of mutation on the natural history (Watkins *et al.* Unpublished). The clinical features of unrelated families sharing a particular mutation can be compared with those of individuals with different mutations within the MHC genes and with those with non-myosin defects, to detect any predictive associations with particular mutation types.

In conclusion, genetic diagnosis in an individual or in a family is becoming a practical proposition and is likely to affect profoundly the management of this condition, both in terms of early diagnosis and risk stratification. Identification of the remaining disease-causing gene(s) in familial hypertrophic cardiomyopathy may be possible by investigating the genes for other cardiac contractile proteins. A complete genetic classification will then be available to determine the full spectrum of manifestations of familial hypertrophic cardiomyopathy. Unresolved issues such as the nature of apparently similar clinical syndromes[17] and the frequency and origins of sporadic disease, will be clarified. Moreover, in addition to the expected clinical benefits of these findings, the documentation of disease-causing mutations in the β cardiac MHC gene will provide insights into myosin structure-function relations that will have impact in wider areas of basic science research.

This work would not have been possible without the cooperation of the family members. We thank K Adams, S Dickie, and A O'Donoghue for help collecting family data. This work was supported by grants from the British Heart Foundation (HW and WM; HW is the recipient of a British Heart Foundation Clinical Scientist Fellowship), National Institutes of Health (HL46320 to JGS, HL41474 and HL42467 to CES), Howard Hughes Medical Foundation (JGS), the American Heart Association (CES), and Bristol Myers Squibb Company.

1 Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;20:1–8.
2 Hollman A, Goodwin JF, Teare D, Renwick JW. A family with obstructive cardiomyopathy (asymmetrical hypertrophy). *Br Heart J* 1960;22:449–56.
3 Jarcho JA, McKenna W, Pare JA, *et al.* Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N Engl J Med* 1989;321:1372–8.
4 Tanigawa G, Jarcho JA, Kass S, *et al.* A molecular basis for familial hypertrophic cardiomyopathy: an alpha/beta cardiac myosin heavy chain hybrid gene. *Cell* 1990; 62:991–8.
5 Geisterfer-Lowrance AA, Kass S, Tanigawa G, *et al.* A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell* 1990;62:999–1006.
6 Greaves SC, Roche AHG, Neutze JM, Whitlock RML, Veale AMO. Inheritance of hypertrophic cardiomyopathy: a cross sectional and M mode echocardiographic study of 50 families. *Br Heart J* 1987;58:259–66.
7 Maron BJ, Nichols PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy:

assessment by M-mode and two-dimensional echocardiography. *Am J Cardiol* 1984;53:1087–94.

8 Maron BJ, Spirito P, Wesley YE, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. *N Engl J Med* 1986; 315:610–4.

9 Antonarakis SE. Diagnosis of genetic disorders at the DNA level. *N Engl J Med* 1989;320:153–63.

10 Solomon SD, Geisterfer-Lowrance AA, Vosberg HP, *et al.* A locus for familial hypertrophic cardiomyopathy is closely linked to the cardiac myosin heavy chain genes, CRI-L436, and CRI-L329 on chromosome 14 at q11-q12. *Am J Hum Genet* 1990;47:389–94.

11 Solomon SD, Jarcho JA, McKenna W, *et al.* Familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. *J Clin Invest* 1990;86(3):993–9.

12 Rosenzweig A, Watkins H, Hwang D-S, *et al.* Preclinical diagnosis of familial hypertrophic cardiomyopathy by genetic analysis of blood lymphocytes. *N Engl J Med* 1991;325:1753–60.

13 Maron BJ, Lipson LC, Roberts WC, Savage DD, Epstein SE. "Malignant" hypertrophic cardiomyopathy: identification of a subgroup of families with unusually frequent premature death. *Am J Cardiol* 1978;41:1133–40.

14 McKenna W, Deanfield J, Faruqui A. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and haemodynamic features. *Am J Cardiol* 1981;47:532–8.

15 Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE. Hypertrophic cardiomyopathy: interrelations of clinical manifestations, pathophysiology, and therapy. *N Engl J Med* 1987;316:780–89 and 844–52.

16 Ciro E, Nichols PF, Maron BJ. Heterogeneous morphologic expression of genetically transmitted hypertrophic cardiomyopathy: two-dimensional echocardiographic analysis. *Circulation* 1983;67:1227–33.

17 McKenna WJ, Stewart JT, Nihoyannopoulos P, *et al.* Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass. *Br Heart J* 1990;63:287–90.

ABSTRACTS IN CARDIOLOGY

Big people and big hearts

Many echocardiographic examinations and most necropsy reports adopt an arbitrary upper limit for left ventricular mass (allowing a difference for sex) to define the presence of hypertrophy. They do not make adequate allowance for the variation in body size.

Left ventricular mass correlates strongly with body height as was well shown in a previous Framingham study by Levy and colleagues (*American Journal of Cardiology* 1987;59:956–60). A further study reported in the abstract below shows that even after adjustment for height there remains an independent strong positive association with body weight. Thus obese subjects have unduly large and heavy left ventricles. These data raise questions about what should be regarded as "normal" and what as "hypertrophy". Perhaps more important is the question whether the increased left ventricular mass in obese subjects is a cause of excess mortality.

MJ DAVIES

The impact of obesity on left ventricular mass and geometry: The Framingham Heart Study

Michael S Lauer, Keaven M Anderson, William B Kannel, Daniel Levy

Objective.—To determine the relationship of varying degrees of obesity with left ventricular mass and geometry.

Design.—Survey.

Setting.—Population-based epidemiologic study.

Participants and Methods.—M-mode echocardiograms, which were adequate for estimation of left ventricular mass, were obtained in 3922 healthy participants of the Framingham Heart Study. Measured height and weight were used to calculate body-mass index, a measure of obesity.

Results.—Body-mass index was strongly correlated with left ventricular mass. After adjusting for age and blood pressure, body-mass index remained a strong independent predictor of left ventricular mass, left ventricular wall thickness, and left ventricular internal dimension ($P < 0{\cdot}01$ for all). Body-mass index was associated with prevalence of echocardiographic left ventricular hypertrophy, particularly in subjects with a body-mass index exceeding 30 kg/m^2.

Conclusions.—Obesity is significantly correlated with left ventricular mass, even after controlling for age and blood pressure. The increase in left ventricular mass associated with increasing adiposity reflects increases in both left ventricular wall thickness and left ventricular internal dimension.—*JAMA* 1991;266:231–36.

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ORIGINAL ARTICLES

QT dispersion in sinus beats and ventricular extrasystoles in normal hearts

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Abstract

***Objective*—Recent studies have suggested that QT interlead variability (dispersion) on the surface electrocardiogram may have potential as a measure of recovery time dispersion. To test this hypothesis further QT dispersion occurring in sinus beats was compared with that in ventricular extrasystoles.**

***Design*—Simultaneous electrocardiograms were recorded at 50 mm/s during sinus rhythm in a drug free state while ventricular extrastimuli were introduced by programmed right ventricular stimulation at different coupling intervals. QT dispersion, defined as the difference between the maximum and minimum QT, was calculated separately for the extrasystoles and preceding and following sinus complexes. To correct for the influence of the number of measurable leads on QT dispersion, an "adjusted" QT dispersion calculated as QT dispersion/square root of the number of measurable leads, was used to compare sinus complexes and extrasystoles.**

***Patients*—Nine patients were studied who were undergoing electrophysiological study for investigation of palpitation and were found to have electrically normal ventricles.**

***Results*—At all coupling intervals tested "adjusted' QT dispersion was significantly greater in the ventricular extrasystoles than in either the preceding or following sinus complexes. For the coupling interval 350 ms, the 95% confidence intervals for the difference between means was 52 to 78 ms (preceding sinus complex) and 56 to 82 ms (following sinus complex) ($p < 0.00001$). There was no correlation between the coupling interval and the magnitude of the "adjusted" QT dispersion.**

***Conclusion*—These results accord fully with expected differences in ventricular recovery time dispersion and offer further support for the hypothesis that QT dispersion reflects regional variation in ventricular recovery. If substantiated by invasive studies, these findings have wide implications for both the usefulness and the method of QT measurement.**

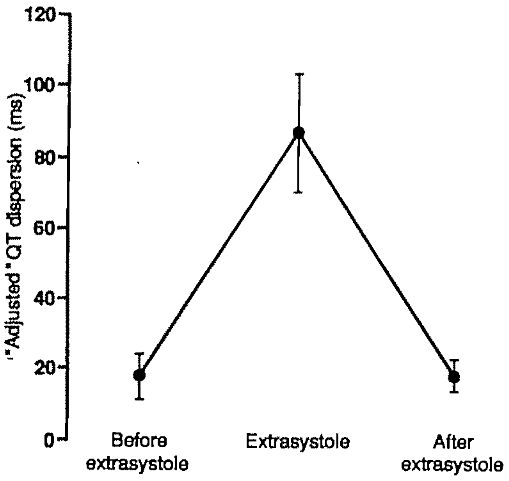
As early as 1887 the QT interval of the surface electrocardiogram was recognised as a potential measure of electrical recovery in the ventricles.[1] Since then, prolongation of the QT interval has been associated with a risk of arrhythmias,[2] a poor prognosis after myocardial infarction,[3] and drug toxicity[4] and has been regarded as evidence that a cardiac drug has reached its target organ.[5] The QT interval in these circumstances is a measure of the time from the earliest ventricular depolarisation to the latest repolarisation. But both these electrical processes are naturally temporally dispersed. A wave of excitation is followed by a wave of recovery. In an elegant review, Krikler identified the significance of the R-on-T ventricular extrasystole which not uncommonly complicates acute myocardial infarction and which shows that even early in the genesis of the surface electrocardiogram T wave some myocardial areas have regained excitability.[6] Such dispersion of repolarisation is widely acknowledged as a likely substrate for serious ventricular arrhythmias but its existence is not exposed by a simple single measure of QT interval.

Work in our department has addressed whether interlead QT variability on the surface electrocardiogram is reflecting variation in myocardial recovery of excitability. Strong support for that hypothesis has come from analysis of patients with arrhythmogenic QT prolongation and antiarrhythmic QT prolongation[7] and also from survivors of acute myocardial infarction treated with placebo and sotalol.[8] We now report the effect of ventricular extrasystoles on interlead QT varability.

Patients and methods

METHODS

We studied nine patients who were undergoing electrophysiological investigation of palpitation. All were found to have electrically normal ventricles: none had evidence of preexcitation and none had inducible ventricular tachycardia. Continuous simultaneous 12 lead electrocardiograms were recorded at 50 mm/s during sinus rhythm in a drug free state while ventricular extrasystoles were introduced by programmed right ventricular stimulation either 300 ms or 350 ms after the preceding Q wave. A wider range of coupling



"Adjusted" QT dispersion (mean (SD)) in ventricular extrasystoles (coupling interval 350 ms from preceding Q wave) and preceding and following sinus complexes. "Adjusted" dispersion was calculated as the difference between maximum and minimum QT divided by the square root of the number of measurable leads.

intervals from 280 ms to 400 ms was also tested in six of the patients. Ten sinus complexes separated the differently timed ventricular extrasystoles.

QT measurements were performed by one observer using a digitiser (CALCOMP 9000). All electrocardiograpic analysis was performed after the studies were completed. QT intervals were measured from the onset of the QRS to the end of the T wave (defined as its return to the T-P baseline) in the last completed sinus complex preceding the ventricular extrasystole and the first sinus complex following the ventricular extrasystole. When U waves were present, the QT was measured to the nadir of the curve between the T and U wave. For the ventricular extrasystoles the interval between the pacing spike and the end of the T wave was measured. QT dispersion, defined as the difference between maximum and minimum QT, was calculated separately for the ventricular extrasystoles, the preceding sinus complexes and the following sinus complexes. QT measurements were performed only in those leads where the T wave end could be reliably identified. In a previous study we showed that QT dispersion values are directly proportional to the square root of the number of measurable leads and derived an "adjusted" QT dispersion calculated as QT dispersion divided by the square root of the number of measurable leads to correct for this influence.[8] Accordingly, for statistical analysis, this "adjusted" QT dispersion was calculated and used to compare the dispersion occurring in sinus complexes and ventricular extrasystoles.

Student's paired *t* test was used to compared the mean "adjusted" QT dispersion occurring in sinus complexes and ventricular extrasystoles. Confidence intervals were calculated for the differences between means.

Table 1 "Adjusted" QT dispersion (mean (SE)) in ventricular extrasystoles and preceding and following sinus complexes

	"Adjusted" QT dispersion (ms)		
Coupling interval	*Preceding sinus complex*	*Ventricular extrasystole*	*Following sinus complex*
300	22 (2)	80 (4)	23 (6)
350	18 (2)	87 (6)	18 (2)

"Adjusted" dispersion was calculated as the difference between maximum and minimum QT divided by the square root of the number of measurable leads.
The coupling interval is the interval between the ventricular extrasystole and preceding Q wave.

Results

Table 1 and the figure show the results of QT dispersion analysis of sinus complexes and ventricular extrasystoles for the coupling interval 350 ms. The mean "adjusted" QT dispersion of the ventricular extrasystole was significantly greater than that of either the preceding or following sinus complex ($p < 0{\cdot}00001$) with 95% confidence intervals for the difference between means of 72 to 78 ms (preceding sinus complex) and 56 to 82 ms (following sinus complex). There was no difference in "adjusted" dispersion between preceding and following sinus complexes. Similar results were obtained for the coupling interval 300 ms (also shown in table 1).

Table 2 shows the results of "adjusted" QT dispersion occurring in ventricular extrasystoles at a range of different coupling intervals. There was no correlation between the "adjusted' QT dispersion and the coupling interval, although for each interval the dispersion of the ventricular extrasystole was at least three times greater than that of either the preceding or following sinus complex. In an attempt to correlate the magnitude of QT dispersion with the timing of the ventricular extrasystole in relation to the state of ventricular recovery we calculated the "prematurity index" expressed as the ratio of the coupling interval to the QT interval of the normal beat or R-R/QT_{max},[9] for each electrocardiogram (data not shown). There was no correlation between this "prematurity index" and "adjusted" QT dispersion.

Discussion

These results are a third piece of evidence that interlead QT variability as measured on the 12 lead electrocardiogram is not merely a technical artefact but probably reflects dispersion of recovery of ventricular excitability. The adjusted QT dispersion of ventricular estrasystoles far exceeded that of the preceding or succeeding sinus complexes. Ventricular extrasystoles most certainly involve dispersion and disruption of activation, and some of the measured QT variation must be attributed to this aspect. The lack of a positive correlation between the ventricular extrasytole coupling interval and the measured dispersion suggests that activation disturbances were the predominant factor contributing to the QT dispersion. This is supported by the fact that irrespective of short coupling intervals producing what were tantamount to R-on-T ventricular extrasystoles the configuration of induced extrasystoles and stimulus to onset times were independent of the coupling interval. The increased dispersion of activation times will also lead to increased dispersion of action potential durations depending on electrical restitution, but if this were the major factor producing QT dispersion then dispersion would have been expected to vary with coupling interval. Our work in humans accords with animal studies in

Table 2 "Adjusted" QT dispersion in ventricular extrasystoles at varying coupling intervals

	"Adjusted" QT dispersion (ms)					
Coupling interval (ms)	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
280	—	118	—	78	—	72
300	57	95	—	75	81	101
320	—	120	72	95	101	57
350	72	113	78	66	75	78
360	78	124	107	72	95	121
400	69	78	98	61	66	107

See footnote to table 1.

which temporal dispersion of ventricular recovery was increased considerably more by a ventricular extrasystole than by a sinus complex.[10] In these experiments increased dispersion of ventricular activation times rather than increased dispersion of action potential durations was responsible for the difference.

Our investigations showed that the QT dispersion of the first sinus complex after the ventricular extrasystole was almost identical to that of the sinus complex preceding the extrasystole. Thus despite the important electrical pertubations caused by the ventricular extrasystole, the electrophysiology of the ventricle returned to the pre-ventricular extrasystole conditions within a single cardiac cycle in these patients with normal hearts. This finding supports the concept of "T wave memory" whereby the characteristics of electrical recovery are retained except in the face of prolonged and consistent abnormalities of activation.[11,12]

The methods we used may have been flawed. Surface electrocardiographic QT measurement is subject to errors but previous work has shown that variation in interlead measurements far outweigh inaccuracies introduced by any other factor including interobserver variation.[13] It was obviously impossible to blind the observer to whether the complex being measured was sinus or extrasystolic but the large differences in QT dispersion between the two types of complex seem unlikely to be explained by observer bias alone. There are potential problems in comparing the dispersion of sinus initiated QRS complexes with that of QRS complexes induced by a pacing spike. Unlike the pacing spike the onset of the Q wave might be expected to vary between leads according to previously established varations in activation time[14,15]; QT dispersion would then reflect dispersion of action potential durations rather than dispersion of ventricular recovery time. Previous work, however, has shown interlead variation in Q wave onset to be small compared with known regional differences in activation time,[13,16] which is considered to reflect the greater dependence of Q wave onset on global rather than local cardiac events.[16] Thus Q wave onset, like pacing spike onset, is virtually synchronous with the earliest onset of ventricular activation.

Late in the development of one of cardiology's classic tools we have found that the surface electrocardiogram may provide new information. All available evidence is that QT dispersion does reflect underlying regional variations in the recovery of ventricular excitability. If this view is more widely endorsed then a radical revision of QT measurements will be necessary. Classic studies from the past may not survive scrutiny. The only scientifically acceptable QT information that would be obtained from a 12 lead electrocardiogram would be either the maximum measured QT interval (implying a search for this on all 12 leads of the surface electrocardiogram) or dispersion of QT intervals.

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1 Waller AD. A demonstration on man of electromotive changes accompanying the heart's beat. *J Physics* 1887;8:229.
2 Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. *Am Heart J* 1975;89:378–90.
3 Ahnve S, Helmers C, Lundman T, Rehnqvist N, Sjogren A. QTc intervals in acute myocardial infarction: first year prognostic implications. *Clin Cardiol* 1980;1980;3:303–8.
4 Fraser AG, Ikram S. Torsade de pointes with prenylamine: do we still need the drug? *Lancet* 1986;ii:572.
5 Edvardsson N, Hirsch I, Emanuelsson H, Ponten J, Olssen SB. Sotalol induced delayed ventricular repolarisation in man. *Eur Heart J* 1980;1:335–43.
6 Krikler DM. A fresh look at cardiac arrhythmias. Pathogenesis and presentation. *Lancet* 1974;i:913–8.
7 Day CP, McComb JM, Campbell RWF. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990;63:342–4.
8 Day CP, McComb JM, Matthews J, Campbell RWF. Reduction in QT dispersion by sotalol following myocardial infarction. *Eur Heart J* 1991;12:423–7.
9 Lown B, Klein MD, Hershberg PI. Coronary and precoronary care. *Am J Med* 1969;46:705–24.
10 Kuo CS, Amlie JP, Munakata K, Reddy CP, Surawicz B. Dispersion of monophasic action potential durations and activation times during atrial pacing, ventricular pacing, and ventricular premature stimulation in canine ventricles. *Cardiovasc Res* 1983;17:152–61.
11 Franz MR, Bargheer K, Rafflenbuel W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardograms: direct evidence for the genesis of the T wave. *Circulation* 1987;75:379–86.
12 Costard-Jöckle A, Franz MR. Dispersion of repolarisation followingm ectopic ventricular pacing [abstract]. *Eur Heart J* 1989;10:24.
13 Cowan JC, Yusoff K, Moore M, *et al.* Importance of lead selection in QT interval measurement. *Am J Cardiol* 1988;61:83–7.
14 Cowan JC, Hilton CJ, Griffiths CJ, *et al.* Sequence of epicardial repolarisation and configuration of the T wave *Br Heart J* 1988;60:424–33.
15 Spach MS, Barr RC. Ventricular intramural and epicardial potential distributions during ventricular activation and repolarisation in the dog. *Circ Res* 1975;37:243–57.
16 Mirvis DM. Spatal variation of QT intervals in normal persons and patients with acute myocardial infarction. *J Am Coll Cardiol* 1985;5:625–31.

Br Heart J 1992;67:42–6

Electrical restitution in the endocardium of the intact human right ventricle

John M Morgan, David Cunningham, Edward Rowland

Abstract

***Objective*—To characterise electrical restitution in the intact human heart.**

***Patients and Methods*—A series of monophasic action potential electrical restitution curves were constructed from a single right ventricular endocardial site in eight patients (three men) without structural heart disease aged 52–68 (mean 55 years). A combination pacing/monophasic action potential electrode was used to pace and record monophasic action potentials at drive cycle lengths of from 350 ms to 1500 ms. Ventricular extrastimuli were delivered at 20 cycle intervals and decreased from the longest coupling interval attainable without escape beats.**

***Results*—Restitution curves shifted downward and towards the left; steady state action potential duration shifted from the restitution plateau and descended the curve, the amount of shift being linearly related to drive cycle length in two patients in whom the relation could be assessed; the amount of monophasic action potential shortening was a function of the degree of prematurity and that relation was unaffected by drive rate; the magnitude of restitution and the time constant of the restitution curve were not changed significantly by altered drive cycle length.**

***Conclusion*—In the intact heart in vivo, electrical restitution (of the monophasic action potential) has similar characteristics to those (of the transmembrane action potential) in cellular preparations in vitro. Thus the alteration of action potential plateau currents by instantaneous rate change or drug effects, which can be directly observed by techniques available to the cellular electrophysiologist, may be indirectly assessed in vivo by characterisation of the effect of these on electrical restitution.**

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The action potential of a myocardial cell achieves a constant duration when the frequency of its depolarisation is constant but shortens instantaneously if a premature extrastimulus is delivered.[1] This has relevance to the mechanism of ventricular tachycardia induction by the delivery of a premature extrastimulus during clinical electrophysiology study, when action potential shortening and the altered velocity of conduction may contribute to the initiation of a reentry circuit.[2-4]

The electrical restitution curve relates the amount of action potential shortening to the prematurity of an extrastimulus.[5] That relation has been characterised by the transmembrane action potential recording in in vitro preparations[5 6] and has also been investigated in the intact human heart in vivo using the monophasic action potential.[7-9] In retrospect, these latter studies had drawbacks because investigators were unable to determine the duration of the monophasic action potential at the site of stimulation (so introducing conduction delay after premature ventricular extrastimulation which may have limited shortening of the diastolic time interval),[7-9] because only one[8 9] or two[7] drive rates were used within individuals or because restitution curves were constructed with extrastimulus coupling intervals that were too long to chart accurately the sharp descent of the restitution curve.[8]

The purpose of this investigation was to use a "combination" monophasic action potential recording/pacing electrode[10] to characterise electrical restitution in the intact heart at a series of drive rates in a manner analogous to the characterisation of electrical restitution in single cell preparations.[6] The clinical relevance of these observations is discussed.

Patients and methods

Eight patients (three male) aged 52–68 (mean 55 years) undergoing electrophysiology study of either atrioventricular reentrant tachycardia or sinus node disease but without evidence of structural heart disease on echocardiography or exercise stress testing at high workload were recruited for this study. All patients gave informed consent for the study protocol which had been approved by the ethics committee of the National Heart and Chest Hospitals.

TECHNIQUE

Patients were studied in the resting post-absorptive unanaesthetised state. Femoral venous access was obtained by a modified Seldinger technique and two 6F introducers were inserted into the right femoral vein. A combination electrode (EP Technologies, Mountain View, California, USA) to measure the monophasic action potential was passed to the right ventricle under fluoroscopic control. The position of the combination electrode was adjusted to give satisfactory monophasic action potential signals. The threshold for

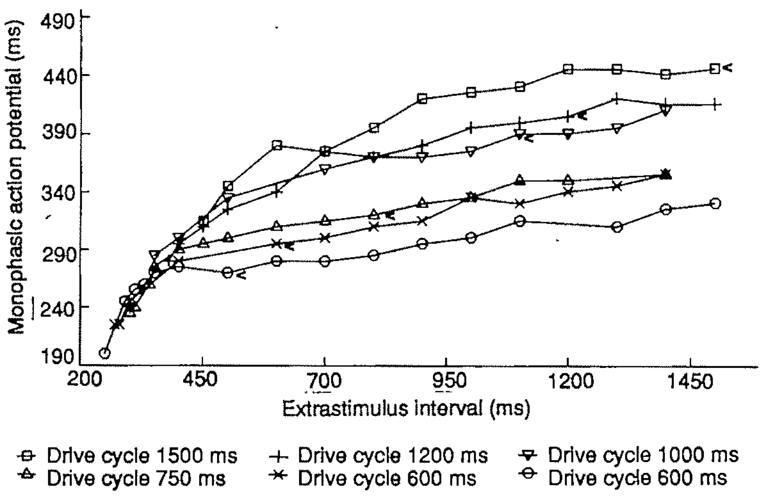

Figure 1 A series of electrical restitution curves constructed at a right ventricular endocardial site; drive cycle lengths ranging from 500 ms to 1500 ms.

ventricular pacing with the combination electrode was determined and ventricular pacing was performed at twice diastolic threshold with a programmed stimulator (Biotronik, Berlin, Germany). All monophasic action potential signals were recorded for analysis at a paper speed of 100/200 mm/s on an inkjet recorder (Siemens Elema Mingograf, Sweden).

STUDY PROTOCOL

A series of electrical restitution curves was constructed in individuals at a single right ventricular endocardial site and at incremented drive cycle lengths. Ventricular pacing was performed for two minutes at each drive cycle length to establish a steady state. Thereafter, ventricular extrastimuli were delivered at twenty cycle intervals, reducing the coupling interval in decrements of 40 ms, 20 ms and 10 ms from the drive cycle length until refractoriness was encountered. We confirmed that the twenty cycle interval between extrastimuli was adequate to allow maintenance of a steady state background upon which to deliver extrastimuli (despite perturbation by the premature stimulus) by measurement of the monophasic action potential duration preceding premature stimulation, which was found to remain constant throughout. Extrastimuli were also delivered at twenty cycle intervals with an increased coupling interval from the drive cycle length by allowing one second intervals between drive trains until escape beats occurred. In this way electrical restitution curves were constructed in a manner similar to that previously described in the investigation of electrical restitution in cellular preparations.[5,6]

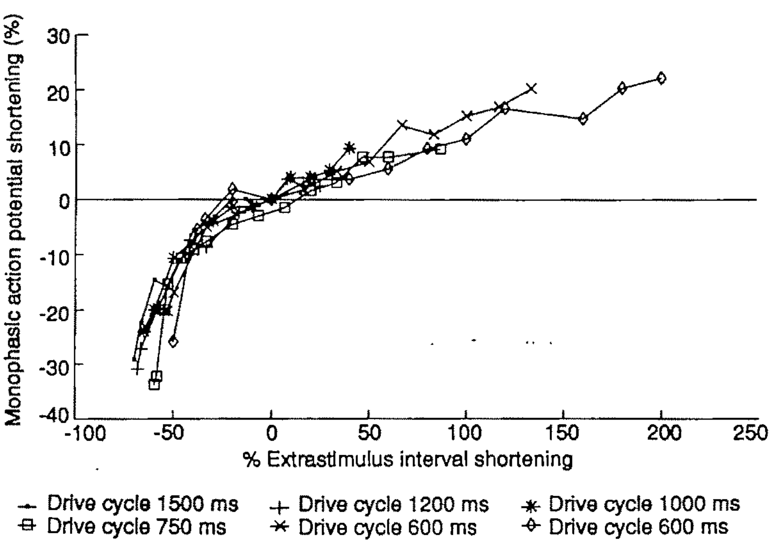

Figure 2 "Site-specific" restitution curve; percentage change in premature monophasic action potential duration from steady state monophasic action potential duration plotted against percentage change in extrastimulus coupling interval from drive cycle length for all electrical restitution curves shown in figure 1.

DATA AND STATISTICAL ANALYSIS

Monophasic action potential durations were determined at 90% repolarisation.[11] Magnitude of restitution was defined as the difference between the monophasic action potential duration elicited by the shortest extrastimulus coupling interval that elicited a propagated response and the monophasic action potential duration on the plateau of the electrical restitution curve. The maximum percentage shortening of the monophasic action potential from the steady state monophasic action potential duration was determined at each drive rate and compared within individuals. Electrical restitution curve time constants were obtained by fitting simple exponential curves to the electrical restitution curves at each drive rate.[6]

In all patients curves were constructed at 400 ms, 500 ms, 600 ms, and 700 ms drive cycle lengths and differences in restitution curve magnitude, maximum percentage action potential shortening, and time constant of restitution were compared between these drive rates by the Kruskal-Wallis test and significance was taken as $p < 0.05$.

Results

Restitution curve series (4–7 curves) were obtained over a range of drive cycle lengths from 350 ms to 1500 ms. In all patients' restitution curve series the following characteristics were identified.

Restitution curves shifted downwards and to the left with increasing drive rate (fig 1). Restitution curves were biphasic in all individuals, though the duration of the "supernormal" action potentials, and therefore the height of the restitution "hump", varied between individuals. However, in all instances it was small compared with the magnitude of the restitution curve (<20%). There was also variation in the size of the restitution "hump" within individuals so that "supernormal" action potentials were longer at faster drive rates in some and at intermediate or slower drive rates in others.

For any given percentage decrease (from drive cycle length) of extrastimulus coupling interval there was a corresponding percentage shortening of monophasic action potential duration (from steady state duration) that was

Table 1 Magnitude of restitution curves at various drive rates in eight patients

	Drive cycle length (ms)											
Patient	1500	1200	1000	900	800	750	700	600	500	450	400	350
1	130	135	125			135	135	120	130		125	
2							35	55	55		40	
3							60	70	80		70	
4				60	45		40	50	70		45	
5				85			85	95	90		90	
6							110	100	90		110	100
7							50	40	45	40	45	50
8							90	85	95		100	

independent of drive rate and characteristic of a particular site (fig 2).

With increasing drive rate the steady state monophasic action potential duration shifted along the restitution curve plateau towards the shoulder of the curve, although the drive rates used were not sufficiently fast to cause the monophasic action potential duration to approach the sharp descent of the electrical restitution curve (fig 1).

The magnitude of the restitution curve did not change significantly with increasing drive rate within patients (table 1).

The maximum percentage shortening of monophasic action potential duration after the most premature extrastimulus that elicited a propagated response did not change significantly with increasing drive rate (table 2). Simple exponential curves were fitted to the electrical restitution curves (correlation coefficients ranging from 0·85 to 0·96) and the time constants of these were not significantly different within individuals (ranging from 0·5 s to 1·3 s).

In two patients sufficient electrical restitution curves were constructed over an appropriate range of drive cycle lengths to allow determination of the relation of the difference between the steady state action potential duration and the duration of the monophasic action potentials on the electrical restitution curve plateau with drive cycle length. This relation was linear at shorter drive cycle lengths and terminated in a plateau at longer drive cycle lengths as the steady state action potential duration moved onto the restitution curve plateau from the shoulder of the restitution curve (fig 3).

Discussion

After Gettes *et al* described shortening of the action potential duration after premature extrastimulation,[1] Bass characterised action potential shortening after premature extrastimulation as electrical restitution[5] and evidence has since been found that electrical restitution is determined by slow recovery of plateau currents from the processes of activation and inactivation[12 13] (although others have suggested that potassium accumulation in the extracellular clefts may also have a role.[14]

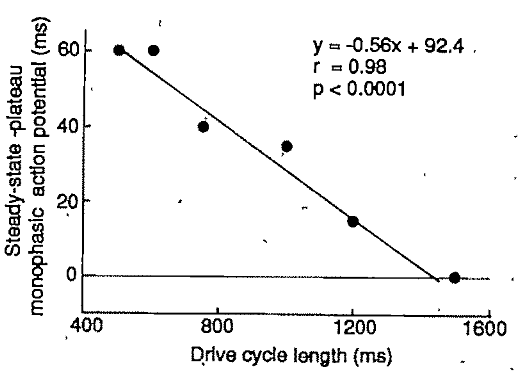

Figure 3 Plot of difference between steady state monophasic action potential duration and monophasic action potential duration on the plateau of the electrical restitution curve against drive cycle length for the series of electrical restitution curves shown in figure 1.

Table 2 Maximum percentage shortening from steady-state monophasic action potential duration during construction of electrical restitution curves at various drive rates in eight patients

	Drive cycle length (ms)											
Patient	1500	1200	1000	900	800	750	700	600	500	450	400	350
1	29	30	29			36	35	25	32		35	
2							13	16	22		17	
3							16	23	24		23	
4				22	18		19	22	33		33	
5				25			33	41	41		45	
6							29	28	27		32	38
7							11	8	8	9	9	12
8							33	33	35		34	

The influence of drive rate on electrical restitution in cellular preparations has been characterised by Boyett and Jewell[5] with further observations made by Boyett and Fedida[15] who have shown that an increase in drive rate causes the electrical restitution curve to shift down and to the left: down because the steady state action potential has adapted at a higher rate to a shorter duration and to the left because incomplete recovery of the action potential plateau currents causes the steady state action potential duration to move from the restitution curve plateau towards the shoulder of the curve.

Franz and colleagues[7 8] and Seed and colleagues[9] used the monophasic action potential recording technique to investigate electrical restitution in the intact human heart. Both groups demonstrated shortening of the monophasic action potential after premature ventricular extrastimulation. Franz and colleagues found that an increase in drive rate caused electrical restitution curves to shift to the left and downwards as in cellular preparations[5 15] but they compared only two drive rates and performed ventricular pacing in only two patients.[7] They also reported that electrical restitution curves could be biphasic with a phase of "supernormal" action potentials before the descent of the restitution curve and repeated this observation in a later report.[8] "Supernormal" action potentials have also been noted on transmembrane action potential recordings from preparations of both human and animal hearts[5 16–19] but not in other species[6 13] and it is suggested there may be species differences.[20 21] Possible mechanisms of "supernormal" action potentials have been suggested. Bass[5] and Greenspan and colleagues[16] have suggested that a low calcium transient, caused by incomplete mechanical restitution after premature extrastimulation, results in increased inward calcium currents which maintain the action potential plateau and therefore prolong action potential duration. Iinuma and Kato[22] reported that calcium channel blocking agents suppress supernormal restitution and this is cited as evidence for this "calcium theory". The situation is almost certainly more complex because the principal inward current supporting the action potential plateau may be the sodium/calcium exchange current and not inward movement of calcium.[23] However, in the presence of a low internal calcium transient, the fast inward calcium current may be greater in amplitude and duration[24] and could therefore support a longer action potential duration during the early restitution phase than that determined by recovery of plateau currents alone. However, Seed and colleagues did not find that electrical restitution was biphasic[9] but this may have been because of the size of the decremented coupling interval that was used to plot the electrical restitution curve.

We found that the restitution curve is displaced downwards and to the left at faster drive rates and that the steady state action potential duration moves towards the shoulder of the restitution curve. However, in contrast to the observations of Boyett and Jewell,[6] the difference in the magnitude of the restitution curve did not decrease significantly with increasing drive rate. Similarly, the time constants of the restitution curves did not change significantly with increasing drive rate in this work whereas Boyett and Jewell reported an increase in the time constant with increasing drive rate.[6] However, the range of drive rates (minimum 350 ms and maximum 1500 ms drive cycle length) that could be used in this in vivo study in the intact human heart was narrower of necessity than that used in the investigation of electrical restitution in vitro (from 0·25 beats/min to 220 beats/min) and this constraint may explain these discordant observations. Also a phase of "supernormal" restitution was observed immediately after the plateau phase in all curves and in all patients although the increase in monophasic action potential duration varied with drive rate within and between individuals. This suggests that the phenomenon is influenced by the degree of prematurity, the background drive rate, and perhaps other site-specific factors.

We suggest that these observations are relevant to clinical electrophysiology because ventricular tachycardia study protocols use premature ventricular extrastimulation during ventricular drive pacing to induce ventricular arrhythmia.[25 26] A suggested mechanism of ventricular tachycardia induction after premature ventricular extrastimulation is creation of a reentry circuit due to slowed conduction, dispersion of refractoriness, or a combination of both.[2-4] There is experimental evidence that altered dispersion of refractoriness or action potential duration contributes to the arrhythmogenic substrate. Kuo and colleagues used a "global hypothermia with regional warm blood perfusion model" to induce disorganisation of repolarisation and observed a critical exaggeration of regional variation in monophasic action potential duration which allowed the induction of sustained ventricular tachycardia with a single extrastimulus.[27] The same group showed in later work that dispersion of the monophasic action potential duration was further exaggerated by a premature extrastimulus though a second premature extrastimulus was required for the induction of ventricular arrhythmia.[28] In earlier work, Han and Moe reported that temporal dispersion of recovery of excitability was minimal in steady state conditions but increased after premature extrastimulation.[29] In the clinical context, it has been suggested that dispersion of refractoriness creates the substrate for arrhythmia, after premature ventricular extrastimulation[30] or a premature extrasystole succeeding a "short-long" sequence.[31] Our own group has also found evidence of abnormal electrical restitution in diseased myocardium.[32]

Thus characterisation of electrical restitution in normal and diseased myocardium may give insight into the contribution of cellular mechanisms to the arrhythmogenic substrate. Furthermore, the drug effect on electrical restitution may characterise some aspects of drug antiarrhythmic properties and recent reports have described the effect of new class II agents on action potential plateau currents.[33] The drug effect on electrical restitution may therefore offer unique opportunities to determine drug action both in vitro and during clinical electrophysiology study in vivo.

In conclusion, electrical restitution in the intact heart (investigated by the monophasic action potential recording technique) resembles electrical restitution in cellular preparations. This may offer a bridge between clinical and cellular electrophysiology, allowing the observations of the cellular electrophysiologist on action potential plateau currents in vitro to be explored in clinical studies in vivo.

1 Gettes LS, Morehouse N, Surawicz B. Effects of premature depolarisation on the duration of action potentials in Purkinje fibers of the moderator band of the pig heart. Role of the proximity and the duration of the preceding action potential. *Circ Res* 1972;30:55–66.

2 Wellens HJJ, Duren DIE, Lie LI. Observations on the mechanisms of ventricular tachycardia in man. *Circulation* 1976;54:237–44.

3 Wit AL, Rosen MR. Pathophysiologic mechanisms of cardiac arrhythmias. *Am Heart J* 1983;106:798–811.

4 Josephson ME, Marchlinski ME, Buxton AE, Waxman HL, Doherty JU, Kienzle MG, *et al.* Electrophysiological basis for sustained ventricular tachycardia—role of reentry. In: Josephson ME, Wellens HJJ, eds. *Tachycardias: mechanisms, diagnosis, treatment.* Philadelphia: Lea and Febiger, 1984:305–52.

5 Bass BG. Restitution of the action potential in cat papillary muscle. *Am J Physiol* 1975;228:1717–24.

6 Boyett MR, Jewell BR. A study of the factors responsible for rate-dependent shortening of the action potential in mammalian ventricular muscle. *J Physiol (Lond)* 1978; 285:359–80.

7 Franz MR, Schaefer J, Schottler M, Seed WA, Noble MIM. Electrical and mechanical restitution of the human heart at different rates of stimulation. *Circ Res* 1983;53:815–22.

8 Franz MR, Swerdlow CD, Bing Liem L, Schaefer J. Cycle length dependence of human action potential duration in vivo. *J Clin Invest* 1988;82:173–80.

9 Seed WA, Noble MIM, Oldershaw P, Wanless RB, Drake-Holland AJ, Redwood D, *et al.* Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). *Br Heart J* 1987;57:32–7.

10 Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM. A new single catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. *J Am Coll Cardiol* 1990;16:878–86.

11 Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG. In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. *Eur Heart J* 1986;7:34–41.

12 Hauswirth O, Singh BN. Ionic mechanisms in heart muscle in relation to the genesis and the pharmacological control of cardiac arrhythmias. *Pharmacol Rev* 1979;30:5–62.

13 Gettes LS, Reuter H. Slow recovery from inactivation of inward currents in mammalian myocardial fibres. *J Physiol (Lond)* 1974;240:703–24.

14 Kline RP, Kupersmith J. Effects of extracellular potassium accumulation and sodium pump activation on automatic canine Purkinje fibres. *J Physiol* 1982;324:507–33.

15 Boyett MR, Fedida D. Changes in the electrical activity of dog cardiac Purkinje fibres at high heart rates. *J Physiol* 1984;350:361–91.

16 Greenspan K, Edmands RE, Fisch C. Effects of cycle-length alteration on canine cardiac action potentials. *Am J Physiol* 1967;212:1416–20.

17 Edmands RE, Greenspan K, Fisch C, Anderson GJ. Correlation between the monophasic action potential and the inotropic response of human myocardium. *Circulation* 1967;36:101–18.

18 Miller JP, Wallace AG, Feezor MD. A quantitative comparison of the relation between the shape of the action potential and the pattern of stimulation in canine ventricular muscle and Purkinje fibres. *J Mol Cell Cardiol* 1971;2:3–19.

19 Noble D, Cohen I. The interpretation of the T wave of the electrocardiogram. *Cardiovasc Res* 1978;12:13–27.

20 Wohlfart B. Relationships between peak force, action potential duration and stimulus interval in rabbit myocardium. *Acta Med Scand* 1979;106:395–409.

21 Elzinga G, Lab MJ, Noble MIM, Papadoyannis DE, Pidgeon J, Seed A, *et al*. The action potential duration and contractile response of the intact heart related to the preceding interval and the preceding beat in the dog and cat. *J Physiol (Lond)* 1981;313:481–500.

22 Iunuma H, Kato K. Mechanisms of augmented premature responses in canine ventricular muscle. *Circ Res* 1979; 44:624–9.

23 Egan T, Noble D, Noble SJ, Powell T, Spindler AJ, Twist VW. Sodium-calcium exchange during the action potential in guinea-pig ventricular cells. *J Physiol* 1989;411: 639–61.

24 Hilgemann DW, Noble D. Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: reconstruction of basic cellular mechanisms. *Proc R Soc Lond* 1987;230:163–205.

25 Waldo AL, Akhtar M, Brugada P, Henthorn RW, Scheinman MM, Ward DE, *et al*. NASPE policy statement: the minimally appropriate electrophysiologic study for the initial assessment of patients with documented sustained monomorphic ventricular tachycardia. *PACE* 1985; 8:918–22.

26 Wellens HJJ, Schuilenburg RM, Durrer D. Electrical stimulation of the heart in patients with ventricular tachycardias. *Circulation* 1972;46:216–26.

27 Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanisms of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983;67:1356–67.

28 Kuo CS, Atarashi H, Reddy CP, Surawicz B. Dispersion of ventricular repolarisation and arrhythmia: study of two consecutive ventricular premature complexes. *Circulation* 1985;72:370–6.

29 Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. *Circ Res* 1964;14:44–60.

30 Mitchell LB, Wyse DG, Duff HJ. Programmed electrical stimulation for ventricular tachycardia induction in humans. I. The role of ventricular functional refractoriness in tachycardia induction. *J Am Coll Cardiol* 1986; 8:567–75.

31 Gomes JA, Alexopoulous D, Winters SL, Deshmukh P, Fuster V, Suh K. The role of silent ischemia, the arrhythmia substrate and the short-long sequence in the genesis of sudden cardiac death. *J Am Coll Cardiol* 1989;14:377–84.

32 Morgan JM, Cunningham AD, Rickards AF, Rowland E. Exaggerated dispersion of repolarisation provoked by premature ventricular stimulation: a mechanism for ventricular arrhythmia [abstract]. *Br Heart J* 1990;64:87.

33 Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K^+ current: Differential sensitivity to block by Class III antiarrhythmic agents. *J Gen Physiol* 1990;96:77–84.

Br Heart J 1992;67:47–52

Value of ambulatory ST segment monitoring in patients with chronic stable angina: Does measurement of the "total ischaemic burden" assist with management?

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Abstract

***Objective*—To assess the prognostic significance of transient ischaemic episodes during daily activities in patients with stable angina.**

***Patients and methods*—172 patients with stable angina attending the cardiac outpatients departments of Hillingdon Hospital (n = 155) and the National Heart Hospital (n = 17) were prospectively studied by exercise testing and 48 hours of ambulatory ST segment monitoring, and followed for prognostic purposes for up to 39 months (mean 24·5 months). Patient inclusion depended on a clinical diagnosis of stable coronary artery disease which necessitated outpatient review (and antianginal treatment in 94% of patients). It was not dependent on objective evidence of reversible ischaemia. Events recorded during the follow up period included death, non-fatal myocardial infarction, unstable angina, and the requirement for revascularisation.**

***Results*—72 patients (42%) had transient ischaemic episodes during daily activities, and 104 patients (60·5%) had an ischaemic response to exercise. 63 patients (36%) had evidence of ischaemia on both investigations; with 59 (34%) having no documented ischaemia on either investigation. There were 27 patient events (15·7%) recorded over a mean 24·5 month follow up, including five deaths (2·9%) (three cardiac related (1·7%)), six non-fatal myocardial infarctions (3·5%), six admissions with unstable angina (3·5%), and 10 revascularisation procedures (5·8%). Of the nine "hard" or objective end points (cardiac death and non-fatal myocardial infarction), only two had evidence of transient ischaemia on ambulatory ST segment monitoring at initial investigation, with 10 of the 25 patients (38·5%) with any cardiac event having such episodes.**

***Conclusions*—The outcome in patients with chronic stable angina receiving standard medical treatment was good over a mean two year follow up period. For the purpose of assessing prognosis over this time scale, there was no advantage to performing ambulatory ST segment monitoring in such patients.**

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Many studies have confirmed that a significant proportion of patients with stable angina have transient ischaemic episodes during their daily activities and that most of these episodes occur in the absence of symptoms.[1-3] It has been shown that the characteristics of silent and painful episodes of transient ischaemia are similar.[4 5] Though there is considerable evidence to suggest that transient ischaemia (predominantly silent) is of adverse prognostic significance in patients with unstable angina[6 7] and in high risk patients after myocardial infarction,[8] there is little information on the prognostic significance of transient ischaemic episodes in patients with chronic stable angina. Two groups have recently reported that the demonstration of transient ischaemia during the daily activities of patients with stable angina helps to identify subgroups at increased risk of developing the end points of coronary disease over a one to two year period;[9 10] however, these studies only included patients with documented evidence of ischaemia on exercise testing, usually at low workloads, and in one study[10] a 23 month cardiac mortality of 15% was reported in patients with angina that was well controlled by treatment. Large scale studies, however, show that overall prognosis in chronic stable angina is generally better than this.[11 12]

We assessed the prognostic significance of transient myocardial ischaemia in patients attending two cardiac outpatient departments with a diagnosis of stable coronary artery disease, for which most had been prescribed suitable antianginal treatment. This population was chosen because it is typical of most patients with angina being treated by their physician.

Patients and methods

One hundred and seventy two patients with stable angina who were attending the cardiac outpatient department of a district general hospital (n = 155) or a tertiary referral cardiac centre (n = 17) were included in the study between February 1988 and August 1989. All were enrolled during a routine outpatient visit. There were 148 men and 24 women (mean age 58·4 years (range 37–78). Seventy five patients (44%) had had a previous myocardial infarction and 23 (13·4%) had undergone coronary artery bypass surgery (n = 21) or percutaneous transluminal coronary angioplasty (n = 2). A total of 141 patients were taking long-acting antianginal medications.

Patients were included in the study if they had stable coronary artery disease which necessitated regular outpatient review. Documented evidence of ischaemia was not a requirement for inclusion, nor was absolute evidence of coronary artery disease. Exclusion criteria included the presence of significant conduction disturbances and medical treatment likely to affect the ST segment.

INVESTIGATIONS

All patients were referred to the National Heart Hospital, where they underwent maximal symptom limited treadmill exercise testing followed by 48 hours of ambulatory ST segment monitoring, which was performed outside the hospital.

Exercise testing

All patients underwent maximal symptom limited treadmill exercise testing according to the modified Bruce protocol.[13] Electrocardiograms were recorded at the onset and every three minutes during exercise and also when significant ST segment depression developed. A test was regarded as positive for ischaemia if there was planar or downsloping ST segment depression of ≥1 mm from baseline measured 0·08 s after the J point, that persisted for three consecutive beats in one or more leads. Exercise was limited by the development of chest pain, breathlessness, exhaustion, intermittent claudication, ventricular arrhythmias, or hypotension.

Ambulatory ST segment monitoring

All patients underwent 48 hours of ambulatory ST segment monitoring outside hospital using pregelled electrodes to record two bipolar leads, an anterior lead (CM5), and an inferior lead. The sites and method of application of these electrodes have been described elsewhere.[14] Two channel recordings were then made onto magnetic tape with a frequency modulated dual channel recorder (Oxford Medilog 2 or MR35). These systems have an adequate frequency response to record and display accurately the ST segment. Tapes were then visually analysed at 60 to 120 times normal speed by an Oxford Medilog MA20 scanner, and all printouts were at 25 mm/s. Significant ST segment depression was defined as a planar or downsloping shift of the ST segment of ≥1 mm measured 0·08 s after the J point and persisting for more than one minute. Significant ST segment elevation was defined as an upward shift of >1 mm of the ST segment measured at the J point and persisting for more than one minute. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes.

During the period of ambulatory monitoring all patients maintained a detailed angina diary, recording the time of each episode of pain, the activity at the onset of symptoms, and the requirement for glyceryl trinitrate. An event marker on the ambulatory monitor was pressed at the onset of symptoms. This marked the magnetic tape so that the electrocardiographic playback would automatically display the electrocardiogram at that time. All patients were encouraged to continue with their normal daily activities during the monitoring period.

ANTI-ANGINAL MEDICATIONS

Patients received standard antianginal medications as prescribed by their attending cardiologist during the period of study. One hundred and forty one patients (82%) received long-acting antianginal treatment. This consisted of a β adrenergic blocking agent (n = 109), a calcium channel blocking agent (n = 60), and long-acting nitrates (n = 88), either singly (n = 54) or in various combinations (double therapy n = 59; triple therapy n = 28; total n = 87). A further 20 patients (11·6%) used short-acting nitrate preparations as required, and 11 patients (6·4%) reported not taking any medications at the time of study.

FOLLOW-UP DATA

Of the 172 patients enrolled in the study, all were reviewed as outpatients as near to or more than two years after inclusion where possible. Where outpatient follow up was not possible, details of patient deaths or clinical state were obtained from the general practitioner or by telephone interview with the patients. For those with events, follow up was taken as the time of occurrence of such episodes. Details of hospital admissions and clinical state over the follow up period were recorded in each case, and a resting electrocardiogram was performed for reasons of comparison to exclude "silent myocardial infarction" over the intervening time. All reported non-fatal myocardial infarctions were confirmed by assessment of the clinical notes and the electrocardiograms and by confirmation of a significant rise (more than twice normal) in cardiac enzymes. Silent myocardial infarction was sought in 138 patients without a recorded event during the follow up period who were reviewed as outpatients.

STATISTICAL ANALYSIS

The three variables (exercise duration, time to angina, and time to ischaemia on exercise) were compared by a one way analysis of variance. Statistical significance was taken to be $p < 0.05$.

Results

One hundred and seventy two patients were studied on an intention to treat basis: 155 (90%) had evidence of coronary artery disease, with reversible ischaemia on exercise testing or ambulatory ST segment monitoring, or prior myocardial infarction, cardiac catheterisation, coronary artery bypass surgery, or coronary angioplasty. A further 17 patients had chest pain suggestive of angina, without having objective evidence of reversible ischaemia.

EXERCISE TESTING

One hundred and seventy two patients underwent maximal symptom limited treadmill exercise testing: 104 (60·5%) had an ischaemic response. The mean total duration of exercise for the whole group was 8·4 minutes, the mean time to ischaemia was 6·3 minutes, and the mean time to angina was 6·4 minutes. One hundred and twelve (65%) patients developed angina during the investigation.

AMBULATORY ST SEGMENT MONITORING

During a total of 7568 hours of ambulatory ST segment monitoring in 172 patients (mean 44 hours), 72 patients (42%) had one or more episodes of transient ST segment change. There were 370 episodes of ischaemia recorded, of which 271 (73%) were silent and 99 (27%) painful. Of the 72 patients, 32 (44%) had only silent episodes, 14 (19%) only painful episodes, and 26 (36%) had both silent and painful episodes.

Figure 1 shows the relation between the results of exercise testing and ambulatory ST segment monitoring. Sixty three patients with ischaemia on ambulatory ST segment monitoring had an ischaemic response during exercise and only nine patients had a negative exercise test but transient episodes of ischaemia during daily activities. Forty one patients had a positive exercise test and no ambulatory ischaemia. A total of 59 patients had no evidence of ischaemia on either investigation. Patients with both tests positive ($n = 63$) had a significantly shorter time to ischaemia on exercise testing than those with only a positive exercise test ($n = 41$) (5·91 *v* 7·23 min, $p < 0{\cdot}02$). Those with both tests positive had a similar maximal exercise time as those with ischaemia only on exercise (7·73 *v* 8·64 min, $p = 0{\cdot}088$). The difference in time to maximal exercise between groups with both tests positive ($n = 63$) and both tests negative ($n = 59$) for ischaemia was statistically significant (7·73 *v* 8·92 min, $p < 0{\cdot}03$).

RELATION OF ISCHAEMIA TO SYMPTOMS ON EXERCISE

One hundred and twelve patients (65%) experienced angina during formal exercise testing. Fifty (80%) of 63 patients with ischaemia both during exercise and daily activities, and 34 (83%) of 41 patients with ischaemia only on exercise testing developed angina during exercise compared with 24 (40%) of 59 patients with no evidence of ischaemia on either investigation.

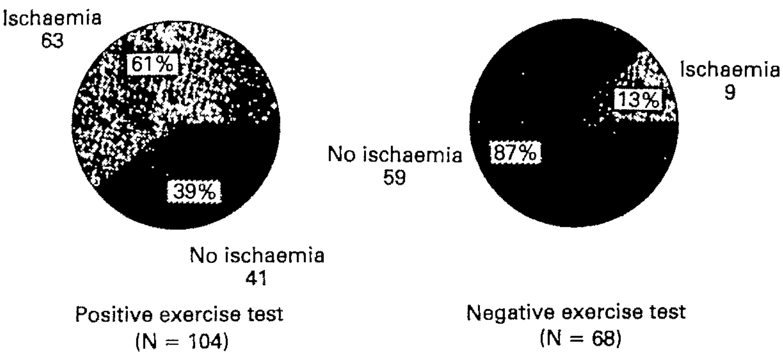

Figure 1 Number of patients with evidence of transient ischaemic change during daily life in association with (n = 104) and without (n = 68) a positive exercise test for ischaemia.

FOLLOW UP DATA

Patients were followed up for a mean of 24·5 months (range 1–39 months), during which time 27 patient events were recorded, of which 25 (14·7%) were cardiac. These are divided into "hard" or objective end points (non-fatal myocardial infarction and cardiac death) and "soft" or subjective end points (unstable angina and revascularisation) where physician diagnosis and decision making influence the event rate.

There were five deaths recorded, three from heart disease and two from malignancy. Six patients had an acute myocardial infarction. A further six patients were admitted to hospital where unstable angina was diagnosed, and 10 patients were referred for revascularisation procedures (bypass $n = 9$, angioplasty $n = 1$), of which nine were performed electively (fig 2).

EVENTS RECORDED

Hard end points

Nine objective end points were recorded (three cardiac deaths and six acute myocardial infarctions) during the 24 month follow up period; four patients showed evidence of ischaemic change on exercise testing, but only two had such evidence during ambulatory monitoring. One patient who died suddenly while driving his car had had frequent episodes of ischaemia during ambulatory monitoring and an ischaemic exercise test, and a further patient with ischaemic changes during both investigations had a non-fatal myocardial infarction. Five of the six patients with non-fatal myocardial infarction had no evidence of ischaemia on either investigation at inclusion in the study.

Soft end points

Six patients were admitted to hospital with unstable angina: four had had a positive exercise test and two had positive tapes, with five of the six having evidence of ischaemia on at least one investigation. Of the 10 patients referred for revascularisation because of symptoms, seven had a positive exercise test and six had positive tapes. Seven had evidence of ischaemia on at least one investigation.

RELATION OF COMBINED ELECTRO CARDIOGRAPHIC FINDINGS TO EVENTS

There were 63 patients with a positive exercise test and evidence of transient ischaemia on ambulatory ST segment monitoring; one patient died and one had acute non-fatal myocardial infarction over the two years of follow up (objective event rate 3·2%). A further patient had unstable angina, and six were referred for revascularisation (total nine patient events (14·5%)). Of the 59 patients with neither test positive, five had an acute non-fatal myocardial infarction (objective event rate 8·5%), one unstable angina, and three were referred for revascularisation (total nine patient events (15·2%)). A further two deaths, four episodes of unstable angina, and one referral for revascularisation occurred in those 50

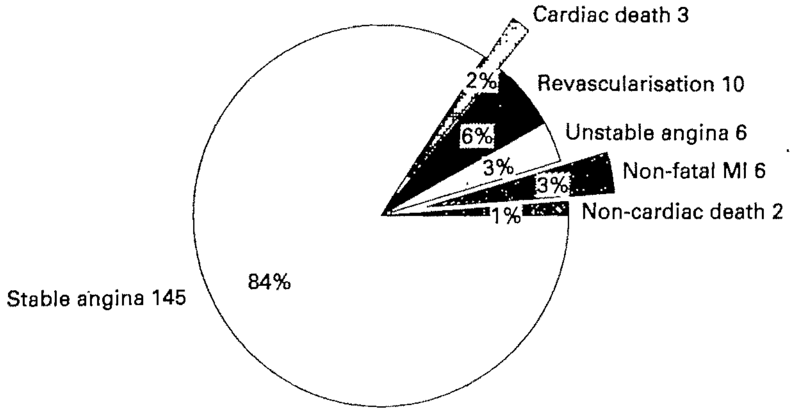

Figure 2 Recorded events in 172 patients with stable coronary artery disease over a 24·5 month follow-up.

patients with one test positive for ischaemia (positive exercise test in all bar one instance) (total seven patient events (14·0%)) (fig 3).

In the 104 patients with a positive exercise test for ischaemia there were nine events in the 63 patients (61%) with ambulatory ischaemia, compared with six events in the 41 patients (39%) without (14·3% *v* 14·7% event rate). Four hard end points (three cardiac deaths and one non-fatal myocardial infarction) were recorded over the follow up period in those with a positive exercise test; two occurred in those with ambulatory ischaemia and two in those without.

FREQUENCY OF "SILENT" MYOCARDIAL INFARCTION

One hundred and thirty eight patients underwent resting electrocardiography at the time of their follow up visit to check for "silent myocardial infarction" over the follow up period (the development of new abnormal Q waves or loss of R wave progression in the precordial leads in the absence of a history of infarction). No electrocardiographic evidence was found in any patient to suggest that such an event had occurred.

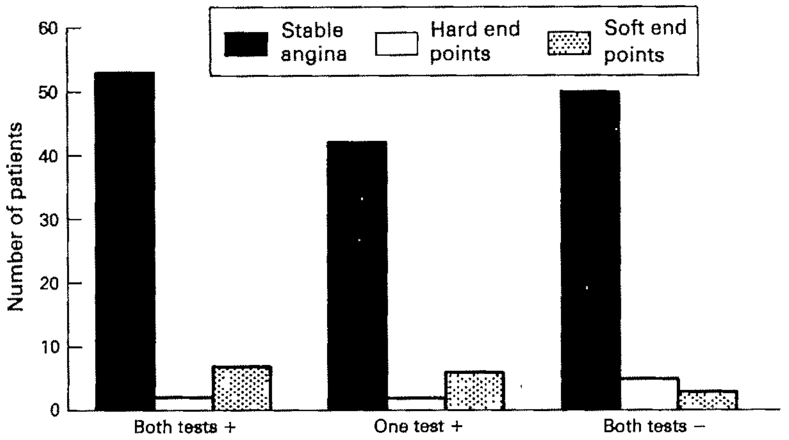

Figure 3 Number of patients with stable angina and frequency of hard (non-fatal myocardial infarction and cardiac death) and soft (unstable angina and requirement for revascularisation) end points over a 24·5 month follow up in those patients with evidence of ischaemia on both exercise testing and ambulatory ST segment monitoring, on neither test, and on one test only.

Discussion

This study confirms that approximately 40% of patients with chronic stable angina receiving standard medical treatment, who were not selected for study on the basis of exercise test results, had episodes of transient myocardial ischaemia during their daily lives, most of which were silent,[15] and it also confirms that exercise testing is a more sensitive investigation than ambulatory ST segment monitoring for the detection of coronary artery disease.[9 10 16] We chose to assess the total ischaemic burden rather than to highlight the significance of silent ischaemia, because silent and painful ischaemia have similar characteristics.[4 5] It is clear that the frequency of such transient ischaemic changes is relatively low in an ambulant population such as this, with only 370 episodes of ischaemia in total being recorded during more than 7500 hours of monitoring during daily activities.

This study also confirms that the medium term prognosis for "unselected" patients with stable angina in the population is very good, with a two year all cause mortality of approximately 3% (cardiac mortality of 1·7%) and an incidence of acute non-fatal myocardial infarction of 3·5%. These figures accord with large prognostic studies in patients with stable angina.[11 12] Brunelli *et al*[11] recently reported on a mean 66 month follow up of 1083 medically treated patients with ischaemic heart disease. Seventy seven per cent had a positive exercise test for ischaemia and 74% had documented significant coronary artery disease: 77% were receiving routine antianginal treatment. They reported an overall annual cardiac mortality rate of 1·54%, rising to 4·1% in those with three vessel disease and up to 5·7% in those with three vessel disease and poor left ventricular function. In the coronary artery surgery study (CASS study),[12] which included assessment of survival in medically treated patients with class I and II stable angina, total annual mortality was 1·6%, rising to 4·0% in the subgroup with three vessel disease and poor left ventricular function.

PROGNOSTIC SIGNIFICANCE OF THE TOTAL ISCHAEMIC BURDEN IN STABLE ANGINA

Previous reports

Recent studies have reported on the prognostic significance of transient episodes of silent ischaemia in stable angina.[9 10 17] Rocco and coworkers in a study of 86 patients with documented coronary artery disease, stable angina, and a positive exercise test for ischaemia, reported that those patients with additional evidence of transient ischaemia during ambulatory ST segment monitoring had an adverse short-term prognosis in terms of the development of unstable angina, acute myocardial infarction, death, or the requirement for revascularisation compared with those without evidence of transient ischaemia.[9] Of the 21 end points recorded (15 unstable angina or revascularisation) during the 12·5 month follow up period, 20 occurred in the 49 patients with transient ischaemic episodes.

Deedwania and Carbajal reported a two year follow up study to assess the prognostic significance of silent ischaemia during daily life for mortality in patients with stable angina.[10] There were 107 patients with long term stable angina in whom symptoms were controlled by standard treatment; 46 (43%) of these had evidence of transient ischaemia during ambulatory monitoring. There were 16 cardiac deaths recorded during the 23 month follow up (three further non-cardiac deaths); 11 occurred in the 46 patients with transient ischaemia during daily life. This represents a 24% cardiac mortality over the follow up period in those with transient ischaemia on ambulatory monitoring and a 15% cardiac mortality for the total group. In the above quoted studies, mean time to ischaemia on exercise testing was 2·9 minutes[9] and 3·3 minutes[10] in those patients who also had changes during ambulatory monitoring, thus they represent highly selected groups of patients.

A further study by Aronow and Epstein reported that 62 (34%) of 185 elderly patients (mean age 82 years) with coronary artery disease had silent ischaemia during daily life and that 65% of such subjects (40 of 62 patients) developed non-fatal or fatal myocardial infarction, ventricular fibrillation, or sudden cardiac death during just over two years of follow up.[17]

The event rates in these studies[9 10] seem high in a group of stable angina patients apparently well controlled by medical treatment, and the results may not be representative of patients with angina in general. Deedwania and Carbajal point out that the vast majority of their patients were unable to complete stage two of the Bruce protocol and might represent a group at higher risk of silent ischaemia and subsequent mortality.[10] Our event rate corresponds with other reports in populations with stable angina, however, it is perhaps surprising that 78% of hard end points occurred in patients without documented evidence of ischaemia during daily life. The apparent lack of association between transient myocardial ischaemia and non-fatal myocardial infarction may be explained in part by the fact that acute myocardial infarction can often result from acute plaque rupture of what were small or medium sized lesions, insufficient to cause prior ischaemic changes. These findings do emphasise the importance of including unselected patients in prognostic angina studies, otherwise the results from highly selected populations may be inappropriately extrapolated to patients with angina in general. While others have shown that silent ischaemia and the total ischaemic burden carries prognostic weight within a subselected group of angina patients who have a demonstrated propensity to exercise ischaemia, usually at low workloads[9 10] we were unable to bear this out in the present study, with only two of 63 patients with both exercise and ambulatory ischaemia dying or having a non-fatal myocardial infarction over a two year period compared with five of 59 patients without evidence of ischaemia having non-fatal myocardial infarction.

Two recent studies have assessed the prognostic significance of ambulatory ischaemia in the stable phase after myocardial infarction[18] and after coronary artery bypass surgery.[19] Tzivoni *et al* studied 224 low risk post-infarction patients, performing ambulatory ST segment monitoring and exercise testing at a mean of two years after infarction. They then followed up these patients for a mean of 28 months.[18] Thirty three per cent (74 patients) had transient ischaemia during ambulatory monitoring (all also had a positive exercise test) and 51% of these had a "cardiac event" during the follow up period compared with 12% of those without transient ischaemia ($p < 0{\cdot}0001$). There was no difference, however, between groups with and without transient ischaemia in terms of the objective end points of cardiac death and acute non-fatal myocardial infarction, the differences being generated by an increased tendency for patients with transient ischaemia to become more symptomatic. These results imply that those with ischaemia on exercise testing and during daily life are more likely to develop symptoms requiring hospital admission or non-medical intervention (subjective end points chosen by physician), but are not more likely to experience a hard end point of coronary artery disease. In the present study 60% of patients referred for intervention because of symptoms had ischaemia on both investigations, thus supporting the findings of Tzivoni *et al.*[18]

Kennedy *et al* also performed ambulatory ST segment monitoring on 184 patients 12 months after coronary artery bypass surgery and noted that at a mean of four years after investigation the presence of transient silent ischaemic episodes had not helped to identify a group more likely to have cardiac events.[19]

POTENTIAL LIMITATIONS OF STUDY

We did not undertake coronary angiography in all patients included in this study and therefore have to accept that all patients may not have had coronary artery disease. To perform a clinically relevant study, however, we included patients on an "intention to treat" basis. In support of this, five of the six non-fatal myocardial infarctions occurred in those without objective evidence of reversible ischaemia.

In an unselected group of patients with stable angina, the two year outcome was favourable, and over this time the results of ambulatory ST segment monitoring seemed to contribute little to the identification of patients liable to have non-fatal myocardial infarction or cardiac death. While assessment of the total ischaemic burden may contribute prognostic information in subsets of patients with coronary artery disease, its true prognostic value in ambulant populations with stable angina must be assessed by performing large medium and long term studies of angina patients on an intention to treat basis, whether or not there is objective evidence of ischaemia. Only then would we be able to establish the precise importance of assessment of silent ischaemia and the total ischaemic burden in the general population of angina patients.

1 Stern S, Tzivoni D. Early detection of silent ischaemic heart disease by 24-hour electrocardiographic monitoring of active subjects. *Br Heart J* 1974;36:481–6.
2 Deanfield JE, Selwyn AP, Chierchia S, *et al.* Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983;i:753–8.

3 Cecchi AC, Dovellini EV, Marchi F, Pucci P, Santoro GM, Fazzini PF. Silent myocardial ischemia during ambulatory electrocardiographic monitoring in patients with effort angina. *J Am Coll Cardiol* 1983;1:934–9.

4 Stern S, Gavish A, Weisz G, Benhorin J, Keren A, Tzivoni D. Characteristics of silent and symptomatic myocardial ischemia during daily activities. *Am J Cardiol* 1988; 61:1223–8.

5 Mulcahy D, Keegan J, Fox KM. Comparative characteristics of silent and painful ischemia during ambulatory monitoring in patients with coronary artery disease. *Int J Cardiol* 1990;28:377–9.

6 Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during two-year follow-up of unstable angina. *J Am Coll Cardiol* 1987;10:756–60.

7 Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 1987;10:1–9.

8 Gottlieb SO, Gottlieb SH, Achuff SC, *et al.* Silent ischemia on Holter monitoring predicts mortality in high-risk post-infarction patients. *J Am Med Ass* 1988;259:1030–35.

9 Rocco MB, Nabel EG, Campbell S, *et al.* Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988;78:877–84.

10 Deedwania PC, Carbajal EV. Silent ischemia during daily life is an independent predictor of mortality in stable angina. *Circulation* 1990;81:748–56.

11 Brunelli C, Cristofani R, L'Abbate A. Long-term survival in medically treated patients with ischaemic heart disease and prognostic importance of clinical and electrocardiographic data. *Eur Heart J* 1989;10:292–303.

12 Vliestra RE, Frye RL, Kronmal RA, Sim DA, Tristani FE, Killip III T, and the participants in the Coronary Artery Surgery Study. Risk factors and angiographic coronary artery disease: a report from the coronary artery surgery study (CASS). *Circulation* 1980;62:254–61.

13 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985;54:321–8.

14 Quyyumi AA, Mockus L, Wright C, Fox KM. Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease: investigation of the frequency of nocturnal ischaemia and coronary spasm. *Br Heart J* 1985;53:186–93.

15 Mulcahy D, Keegan J, Lindsay D, Sparrow J, Park A, Wright C, Fox K. Silent myocardial ischaemia in patients referred for coronary artery bypass surgery because of angina: a comparison with patients whose symptoms were well controlled on medical treatment. *Br Heart J* 1989; 61:496–501.

16 Mulcahy D, Keegan J, Sparrow J, Park A, Wright C, Fox KM. Ischemia in the ambulatory setting—the total ischemic burden: relation to exercise testing and investigative and therapeutic implications. *J Am Coll Cardiol* 1989;14:1166–72.

17 Aronow WS, Epstein S. Usefulness of silent myocardial ischemia detected by ambulatory electrocardiographic monitoring in predicting new coronary events in elderly patients. *Am J Cardiol* 1988;62:1295–6.

18 Tzivoni D, Gavish A, Zin D, *et al.* Prognostic significance of ischemic episodes in patients with previous myocardial infarction. *Am J Cardiol* 1988;62:661–4.

19 Kennedy HL, Seiler SM, Sprague MK, *et al.* Relation of silent myocardial ischemia after coronary artery bypass grafting to angiographic completeness of revascularisation and long-term prognosis. *Am J Cardiol* 1990;65:14–22.

Br Heart J 1992;67:53–6

Limited value of the resting electrocardiogram in assessing patients with recent onset chest pain: lessons from a chest pain clinic

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Abstract

***Objective*—To evaluate a clinic set up specifically to assess patients with recent onset chest pain, particularly those presenting with a normal resting electrocardiogram.**

***Design*—Retrospective review of case notes.**

***Setting*—Cardiac department of a tertiary referral cardiothoracic centre.**

***Patients*—250 consecutive patients with recent onset chest pain seen within 24 hours of general practitioner referral.**

***Outcome measures*—Clinical diagnosis and management.**

***Results*—40% of patients were seen within seven days of the onset of symptoms. Twenty seven per cent had non-cardiac symptoms and could be discharged while 60% were considered to have cardiac pain. Sixty six patients (26%) were admitted directly from the clinic and 48 of these underwent coronary angiography within three weeks. Seventy patients (28%) have so far undergone intervention (angioplasty or coronary artery surgery), 22 within one month of presentation. One hundred and nine patients (44%) presented with a normal resting electrocardiogram, 21 of whom were considered to have unstable angina. Forty one of these patients were investigated of whom 37 were found to have significant coronary disease and 26 have undergone intervention.**

***Conclusions*—This experience highlights the inadequacy of a routine electrocardiogram reporting service in patients with recent onset of chest pain. An alternative facility offering immediate and complete cardiac assessment produced patient benefit with early diagnosis and intervention. Investigation of these patients, however, accounted for 5% of cardiac catheterisation laboratory throughput; this was a significant additional and unscheduled workload.**

The value of the resting electrocardiogram in patients with suspected acute infarction is clear.[1] Its role in the management of patients with recent onset chest pain which may have a cardiac cause, however, is poorly defined. Patients with long-standing symptoms may be referred to a cardiological outpatient department but those with shorter histories need an early diagnosis. Waiting lists for outpatient appointments can result in diagnostic delay in patients with possible unstable coronary disease or unnecessarily prolong anxiety in patients with non-cardiac symptoms. Referral to an accident and emergency department may be viewed as unjustified in patients without acute symptoms and junior casualty department staff may not be sufficiently experienced to make an adequate assessment.[2] These patients are frequently referred to their local hospital for an electrocardiogram, the report of which takes no account of the clinical presentation. Thus this investigation may be misleading or falsely reassuring.

Alternatively, these patients may be offered a complete assessment in a dedicated daily clinic. We established such a facility to assess specifically patients with possible cardiac pain of recent onset and here we report our experience of the first 250 patients seen in this chest pain clinic.

Patients and methods

A chest clinic was established in October 1988 at Harefield Hospital, a regional cardiothoracic centre, which also serves general practitioners responsible for a local population of 150 000. Newly referred outpatients are usually seen within eight weeks and up to 20 such patients are seen weekly. A single cardiac catheterisation laboratory investigates 2200 patients annually and 250 angioplasties and 650 coronary bypass surgical procedures are performed annually. The current wait for diagnostic cardiac catheterisation is between four and six months.

A circular was sent to 120 local general practitioners to inform them of a daily facility offering full assessment of patients presenting with chest pain of recent onset. General practitioners were encouraged to telephone the on-call cardiology registrar to discuss the case before sending the patient to the clinic which was available between 2 and 4 pm every week day.

All patients were seen on the day of referral and assessed by a cardiology registrar or senior registrar who recorded the clinical diagnosis based on the history, physical examination, and resting electrocardiogram.

Unstable angina was defined as any deterioration in the pattern of previously stable symptoms, rest pain, or only exertional symptoms if they had been present for less than two

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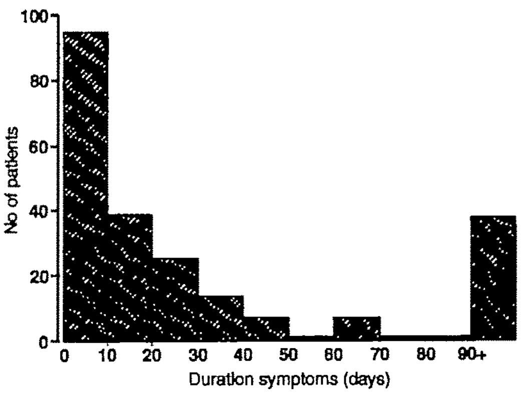


Figure 1 Duration of symptoms in the study group ("90+" indicates patients who had symptoms for more than three months).

weeks. Significant coronary disease was defined angiographically as a 50% or greater reduction in luminal diameter of at least one major coronary vessel.

Further investigations—for example, exercise electrocardiography—or hospital admission, were arranged if appropriate and the diagnosis, action taken, and outcome were recorded and reviewed.

Results

After the establishment of the chest pain clinic in October 1988, 250 patients (176 men and 74 women, mean age 58 years (range 25–84 years)) were assessed over the next 18 months. All patients were seen within 24 hours of referral by their general practitioner.

DURATION OF SYMPTOMS

The mean duration of symptoms precipitating referral was 27 days (range 1–90 days) (fig 1). One hundred and eighty seven patients (75%) presented within 30 days of the onset of symptoms and 100 (40%) were assessed within seven days.

Thirty eight patients (15%) had had symptoms for more than three months with no discernible recent deterioration (fig 1, column 90+ days).

CLINICAL DIAGNOSIS

Sixty nine patients (27·5%) were considered to have non-cardiac pain (fig 2). In a further 29 patients (11·5%) the cause of chest pain was not clear after clinical assessment and further investigations were arranged. In 146 cases (58·5%) the diagnosis was of angina and in half of these the patient's symptoms were considered to represent unstable angina, despite a normal resting electrocardiogram in 21 patients. Six patients (2·5%) presented with myocardial infarction.

Seventy three patients had exercise testing on the day of presentation and in most cases this aided the clinical diagnosis.

PATIENT OUTCOME

Sixty three patients considered to have non-cardiac pain (25·2%) were discharged from the clinic without further follow up. In a further 59 cases (23·6%) arrangements were made for outpatient review with the result of further investigations—for example exercise electrocardiography—or to monitor the effect of changes in medical treatment.

Over half the patients (128 cases, 51·2%) had coronary arteriography, with significant coronary disease being found in 114. Sixty two of these were investigated within 30 days of presentation and 35 were studied within seven days. Sixty six patients (26%) required admission directly to the ward for stabilisation on medical treatment. Of these 48 underwent coronary arteriography within 21 days.

Thirty one patients (12·4%) had coronary artery bypass surgery and 39 (15·6%) coronary angioplasty. These interventions were performed within 30 days of presentation in 22 and within seven days of presentation in nine.

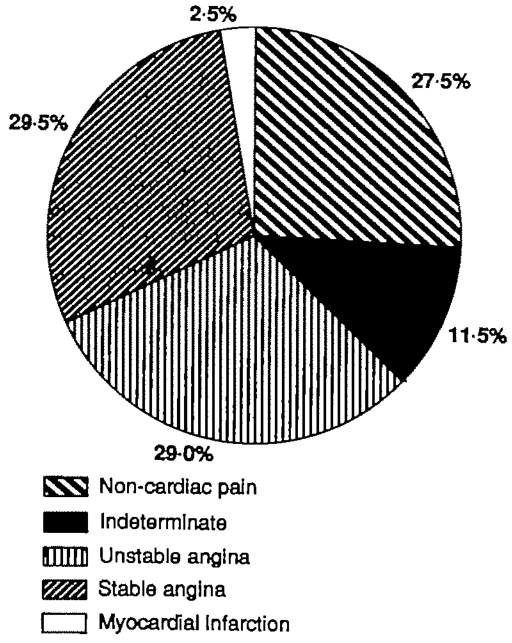


Figure 2 Clinical diagnosis in 250 patients.

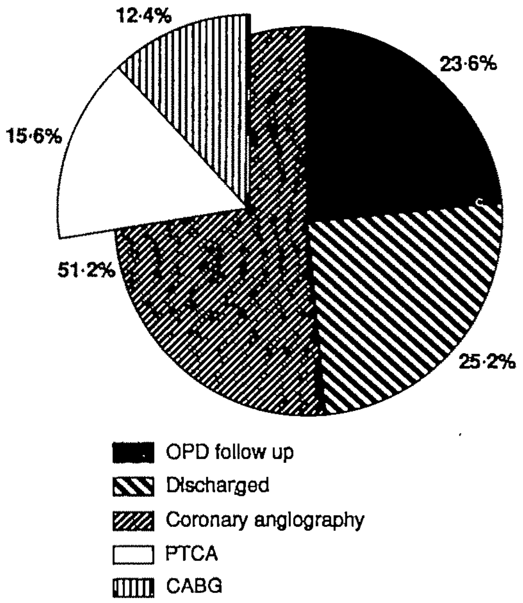
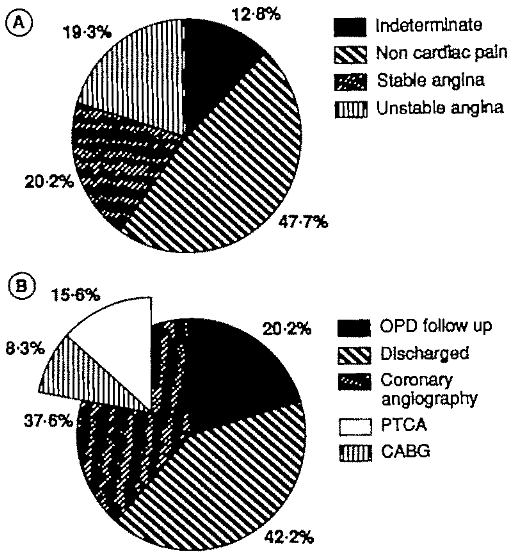


Figure 3 Outcome in 250 patients. CABG, coronary artery surgery; PTCA, percutaneous transluminal coronary angioplasty; OPD, outpatients department.

Figure 4 (A) Clinical diagnosis in 109 patients presenting with a normal electrocardiogram. (B) Outcome in 109 patients presenting with a normal electrocardiogram. See footnote to figure 3 for abbreviations.



DIAGNOSIS AND OUTCOME IN PATIENTS WITH NORMAL ELECTROCARDIOGRAMS

One hundred and nine (44%) patients presented with a normal resting electrocardiogram. In almost half of this group (52 cases, 47·7%) the diagnosis was of non-cardiac pain while in a further 14 cases (12·8%) the cause of chest pain was undetermined (fig 4).

Outpatient follow up was arranged for 22 patients (20·2%) and 46 patients (42·2%) were discharged without further review being planned.

However, in 43 cases (39·5%) the diagnosis was of cardiac pain and despite a normal resting electrocardiogram half of these patients were considered to have unstable angina. Forty one patients (37·6%) in this group had coronary arteriography, which showed significant coronary disease in 37. Coronary angioplasty has been undertaken in 17 patients (15·6%) and coronary artery surgery in nine cases (8·3%).

Discussion

This initial experience of a chest pain clinic suggests that patients with symptoms of recent onset may benefit from early cardiac assessment. Though these data are uncontrolled it is likely that early investigation and intervention in some cases was advantageous. A quarter of our patients had undergone cardiac catheterisation as a definitive diagnostic procedure within one month of presentation. Similarly 10% had undergone either coronary angioplasty or coronary artery surgery within the same period. This is considerably shorter than our routine waiting time for cardiac catheterisation and intervention.

The most important finding in this study was the outcome of patients with normal electrocardiograms. In our study 20% of these were considered to have unstable angina and they constituted almost a third of all patients with that diagnosis. In the absence of electrocardiographic changes the diagnosis in these circumstances must be a clinical one but it is supported by the requirement for either coronary artery surgery or angioplasty in a quarter of our patients with normal electrocardiograms.

This experience highlights the potential dangers associated with the finding of a normal resting electrocardiogram in patients with suspected unstable angina. In a practice serving 2500 patients, a general practitioner may see up to 100 patients with chest pain per year.[3] Our results show that in up to one third of these patients a normal resting electrocardiogram may be seriously misleading and, therefore, the value of a routine electrocardiography reporting service must be questionable. Some general practitioners have access to their own electrocardiograph[4] which may relieve some of the load from hospital departments. However, even their correct interpretation of the electrocardiogram would not avoid the reassurance of a falsely normal result. For the same reasons referral to an accident and emergency department would not confer further advantage.[2]

Patients referred for either coronary arteriography or angioplasty as a result of attending our chest pain clinic accounted for almost 5% of the annual throughput of our cardiac catheterisation laboratory. In the absence of a chest pain clinic it is likely that, eventually, these patients would have required investigation and treatment, thus constituting the same annual load on resources. However, accident and emergency department or outpatient referral in these cases would undoubtedly have led to delay in investigation and treatment. Furthermore these procedures represent an unplanned workload which has important implications in terms of the availability of hospital beds and impact on an already full cardiac catheterisation list.

A diagnosis of acute myocardial infarction was made in only six cases despite referral of patients specifically with suspected cardiac symptoms. However, the population assessed in our clinic was selected after discussion with the general practitioner in each case. Because patients were to be seen in an outpatient department we believed that in those cases where the diagnosis of acute myocardial infarction was likely the general practitioner would be better advised to send the patient to the nearest accident and emergency department. There, full resuscitative facilities would be immediately available on arrival if required.

A quarter of the patients seen had non-cardiac pain. We did not regard this finding as a waste of clinic resources because this provided a valuable service to a sizeable number of patients who required reassurance. A wait for outpatient referral could have engendered unnecessary anxiety; early assessment with exercise electrocardiography, if appropriate, meant that outpatient attendance was then unnecessary.

CLINICAL IMPLICATIONS

In patients with chest pain of recent onset, a normal resting electrocardiogram cannot exclude unstable angina or, in some cases, acute infarction.[5] The value of a routine electrocardiogram reporting service is therefore questionable.

A chest pain clinic run by specifically trained staff offers rapid assessment of patients with suspected cardiac symptoms of recent onset and allows early investigation and intervention if appropriate. However, such a facility has important consequences for hospital resources in terms of bed availability and the workload of the cardiac catheterisation laboratory.

1 Timmis A. Early diagnosis of acute myocardial infarction. *BMJ* 1990;301:941–2.
2 McCallion WA, Templeton PA, McKinney LA, Higginson JDS. Interpretation of electrocardiograms in the accident and emergency department [abstract]. *Br Heart J* 1990; 64:65.
3 Mead M, Paterson H. *Tutorials in general practice*. London: Pitman, 1983.
4 Davies A. Electrocardiographs in general practice. *BMJ* 1989;299:408–9.
5 Yusuf S, Pearson M, Sterry H, *et al*. The entry ECG in the early diagnosis and prognostic stratification of patients with suspected acute myocardial infarction. *Eur Heart J* 1984;5:716–26.

Comment

We all can cite cases where a patient complaining of chest pain had a normal electrocardiogram in Accident and Emergency and was discharged with tragic consequences. Norell *et al* found that 43 of 109 patients with recent onset of chest pain and a normal electrocardiogram subsequently had an unequivocal clinical diagnosis of cardiac pain. In nearly all of them (41) this diagnosis was confirmed at coronary angiography. Subsequently 26—nearly a quarter—of the original group with a normal electrocardiogram had coronary angioplasty or coronary artery surgery. This shows that we must not rely on a normal electrocardiogram to exclude important coronary disease in patients with recent onset of chest pain. Ideally, if resources permit, these patients should be assessed later by exercise testing.

Norell and his colleagues have given us a useful measure of the true size of this potentially dangerous problem. The message is not new to cardiologists but now that we see the size of the problem we must alert general practitioners, general physicians, and junior doctors in casualty departments and remind them that the electrocardiogram and patient should always be examined together.

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"Subclinical" pacemaker syndrome: a randomised study of symptom free patients with ventricular demand (VVI) pacemakers upgraded to dual chamber devices

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Abstract

***Objective*—To determine whether symptom free patients with single chamber pacemakers benefit from dual chamber pacing.**

***Design*—A randomised double blind crossover comparison of ventricular demand (VVI), dual chamber demand (DDI), and dual chamber universal (DDD) modes after upgrading from a VVI device.**

***Setting*—Cardiology outpatient department.**

***Patients*—Sixteen patients aged 41–84 years who were symptom free during VVI mode pacing for three or more years.**

***Intervention*—Pacemaker upgrade during routine generator change.**

***Main outcome measures*—Change in subjective (general health perception, symptoms) and objective (clinical assessment, treadmill exercise, and radiological and echocardiographic indices) results between pacing modes before and after upgrading.**

***Results*—75% preferred DDD, 68% found VVI least acceptable with 12% expressing no preference. Perceived general well-being and exercise capacity ($p < 0{\cdot}01$) and treadmill times ($p < 0{\cdot}05$) were improved in DDD mode but VVI and DDI modes were similar. Clinical, echocardiographic, radiological, and electrophysiological indices confirmed the absence of overt pacemaker syndrome, although mitral and tricuspid regurgitation was greatest in VVI mode ($p < 0{\cdot}01$).**

***Conclusions*—Most patients who were satisfied with long term pacing in VVI mode benefited from upgrading to DDD mode pacing suggesting the existence of "subclinical" pacemaker syndrome in up to 75% of such patients. The DDI mode offered little subjective or objective benefit over VVI mode in this population and should be reserved for patients with paroxysmal atrial arrhythmias.**

VVI mode pacing should be used only for patients with very intermittent symptomatic bradycardia or atrial fibrillation with a good chronotropic response during exercise.

The pacemaker syndrome is a constellation of signs and symptoms arising as a direct result of ventricular demand pacing (VVI mode).[1] The mechanisms of this syndrome are varied and may be the result of haemodynamic, neuroendocrine, and electrophysiological factors.[2–4]

In most cases this syndrome can be cured by dual chamber pacing, which relieves almost all the symptoms.[5] However, there are several reports of "pacemaker syndrome" occurring in dual chamber modes[6 7] (usually explained by adverse programming of atrioventricular delay causing, in effect, ventricular asynchronous pacing).

The incidence of the pacemaker syndrome in VVI paced patients (still the predominant pacing mode used worldwide and in the United Kingdom) has been variously described as 7–25% according to the severity of intolerance of ventricular asynchronous pacing.[8] No study has yet investigated the effect of upgrading VVI devices to dual chamber pacing in apparently symptom free patients.

STUDY AIMS

To assess, by a randomised double blind crossover study the effect of dual chamber pacing in patients with no overt evidence of the pacemaker syndrome after chronic, long-term VVI pacing.

Patients and methods

PATIENTS

We studied 16 patients aged 41–84 years (mean 66·6 years, 69% male). Any patient who was largely symptom free and who felt "generally well" after chronic VVI pacing for at least three years could be enrolled. Table 1 shows the reasons why patients needed a change of pacemaker generator. Patients with chronic atrial flutter or fibrillation, or who were unable to walk on a treadmill were excluded. One patient with a VVIR pacemaker programmed to VVI mode for three years was included.

STUDY DESIGN

This was a prospective randomised double blind crossover comparison of three pacing modes (VVI, DDI, and DDD) after a VVI pacemaker had been upgraded to a dual chamber device in patients expressing no dis-

Table 1 Patient details, pacemaker types, and left ventricular systolic function

Patient	*Sex*	*Age*	*Indication for implant*	*Other associated conditions*	*Pacemaker dependent*	*Date of initial implant*	*Previous pacemaker type*	*Reason for upgrade*	*Upgrade pacemaker type*	*Pacing base rate*	*Peak HR in VVI*	*Peak HR in DDD*	*Mean LV fractional shortening (%)*
1	M	69	SSS + AVIII	MI, PAF	Y	1980	S 625*	EOL	Delta	55	55	115	12
2	M	74	Syncope AVI, AVII		N	1979	ELA 1250	EOL	Cosmos II	70	165	140	42
3	M	75	AVIII	DM, TIAs MI	Y	1979	S 668	EOL	Cosmos II	70	70	88	13
4	F	67	Intermittent AVII, AVIII		N	1977	TE 120B	EOL	Cosmos II	70	126	120	40
5	M	71	AVIII		Y	1982	APC 5251	Faulty reed switch	Cosmos II	70	70	87	20
6	M	41	AVIII	Dilated cardio-myopathy	Y	1976	S 668	EOL	AFP	75	80	145	14
7	M	72	AVIII		Y	1978	C L900	EOL	Cosmos II	70	70	109	23
8	M	77	AVIII		Y	1977	TE 120B	EOL	Cosmos II	70	70	130	21
9	F	65	AVIII		Y	1985	TE 5281	Painful pacemaker site	AFP	70	70	140	36
10	F	57	SSS + AVIII	PHA, PAF	Y	1983	VIT TX*	EOL	AFP	70	70	130	25
11	M	65	SSS + AVIII	Post MVR	Y	1982	S 668	Intermittent myopotential inhibition	Synchrony	70	70	80	21
12	F	74	SNI + AVIII		Y	1978	MD 5927	EOL	Synchrony	70	70	135	35
13	F	69	AVII		N	1978	C L900	EOL	AFP	70	96	110	42
14	M	52	SNI, AVIII		Y	1987	S 688L	Faulty telemetry	Synchrony	70	70	131	25
15	M	84	Intermittent AVIII	Multiple VEs	N	1979	MD 5983	EOL	Paragon	70	78	94	30
16	M	70	SSS + AVIII		Y	1983	S 678B	EOL	AFP	70	70	125	32

*Paced in VVI mode for more than three years before upgrading procedure.
Indication for implantation: SSS, sick sinus syndrome (including paroxysmal supraventricular tachycardia); AVI, first degree heart block; AVII, second degree heart block; AVIII, complete heart block; SNI, sinus node, chronotropic incompetence.
Other conditions: MI, myocardial infarction; PAF, paroxysmal atrial fibrillation; DM, diabetes mellitus; TIA, transient ischaemic attack; PHA, post His bundle ablation; MVR, mitral valve replacement; VE, ventricular extrasystoles.
Pacemaker dependent: Y, predominantly paced rhythm in VVI mode. N, predominately non-paced rhythm.
Reason for upgrade: EOL, end of life.

satisfaction with long term, ventricular demand pacing. Before enrolment all patients underwent a full assessment with their original pacemaker programmed to VVI mode. This was called "VVI pre" mode. If the subjective questionnaire scores suggested symptoms attributable to the "pacemaker syndrome" the patient was excluded from the study at this stage. Postoperatively all patients were programmed to the three study modes in a random sequence (by random number tables). The VVI mode programmed after upgrading was called the "VVI post" mode.

Written, informed consent was obtained from each patient before the upgrading procedure. Programming was undertaken by senior cardiac technicians and full assessment was undertaken after four weeks of out of hospital activity in each mode. After the upgrading neither the patients nor the investigating clinicians were aware of the programmed pacing mode at any time.

PACEMAKER UPGRADING PROCEDURE

The old generator was explanted and the ventricular electrode tested under local anaesthesia. If the ventricular pacing threshold was 2 V or less, with an intracardiac R wave amplitude of 3 mV or more the electrode was retained and adapted to fit an appropriate dual chamber device (table 1). If these criteria were not fulfilled a new bipolar carbon tipped electrode (Siemens-Elema model 1010T/60 (IS1), Siemens-Elema AB, Stockholm, Sweden) was inserted via the subclavian vein and the old electrode was removed. The atrial electrode was inserted via the same subclavian vein and sited in the right atrial appendage in all patients.

All but two patients (1 and 3) underwent intraoperative electrophysiological assessment. This showed normal atrioventricular nodal conduction in three patients (patients 2, 4, and 13) (atrioventricular node Wenckebach cycle length greater than 120 beats per minute)[9]; abnormal sinus node recovery time (SNRT) in five patients (patients 10, 11, 12, 14 and 16) (SNRT greater than 1500 ms, corrected SNRT greater than 550 ms)[10]; and consistent retrograde ventriculo-atrial conduction in four patients (patients 2, 4, 6 and 13).

PACEMAKER PROGRAMMING

Twenty four hours after their pacemaker was upgraded all patients were checked to ensure satisfactory dual chamber pacing and then programmed to the first randomised study mode) at a pacing basic rate identical with that in VVI pre mode. An atrioventricular delay of 150 ms was programmed in the DDD and DDI modes in all patients.

A settling in period of two weeks in the first mode was allowed after implantation and the first four week study period started immediately afterwards. After this study period satisfactory dual chamber pacing function and pacing thresholds were reconfirmed. The pulse amplitude in each chamber was then programmed to twice the pacing threshold and the sensitivity to half the sensing threshold. These variables remained unaltered for the rest of the study.

SUBJECTIVE ASSESSMENT

This consisted of three self administered questionnaires. The first used visual analogue scales to assess the perceived general well-being and exercise capacity. Subjects placed a mark on a 15 cm line from the discrete minimum point signifying "extremely unwell" or "inability to exercise" to the maximum point signifying "extremely well" or "unlimited exercise capacity". The result was expressed as a percentage of the distance from the minimum point to the mark divided by the length of the line.[11 12]

The second questionnaire assessed the patient's perception of their functional capacity by the well validated Specific Activities Scale functional status questionnaire.[13] This grades patients from class I (unlimited physical capacity) to class IV (grossly incapacitated).

The final questionnaire assessed the incidence and frequency of symptoms of mild cardiac failure or pacemaker induced haemodynamic dysfunction that occurs in the pacemaker syndrome.[1] The format of the questionnaire used a quantitative score where: 1 = all of the time, 2 = most of the time, 3 = some of the time, 4 = occasionally, and 5 = none of the time. The "symptom prevalence score" (maximum 84) was calculated by the arbitrary weighting of symptoms (table 2). A score of 25 or more was highly suggestive of the pacemaker syndrome or moderate heart failure.

CLINICAL ASSESSMENT

This was undertaken in all cases by the same clinician (NS) while he was unaware of the patient's programmed mode. The clinical examination was performed after subjective and objective assessment was completed, with patients lying supine on an examination couch with their upper torso at 45°. Table 3 shows the variables assessed and arbitrary clinical assessment score. (Any assessment requiring electrocardiographic evaluation was undertaken by the senior technician assisting in patient monitoring).

Table 2 Symptom prevalence score

	Symptom	*Score*
1	Memory	0–4
2	Concentration	0–4
3	Tiredness	0–8
4	Lightheadedness	0–8
5	Shortness of breath	0–12
6	Orthopnoea	0–12
7	Cough	0–4
8	Palpitation	0–8
9	Fluttering in neck/abdomen	0–8
10	Dizziness	0–8
11	Ankle oedema	0–8
Total score		0–84

Table 3 Clinical indices assessed and the clinical assessment score

	Clinical assessment score
Variability of systolic blood pressure	0–6
JVP cannon waves	0–6
Peripheral oedema	0–6
Pulmonary oedema	0–6
Pulsatile liver	0–2
Variability of heart sounds	0–2
Variability of heart murmur(s)	0–2
Characteristics of heart murmur(s)	0–6
Effect of magnet application to pacemaker on characteristics of murmur(s)	0–6
Extent of retrograde V-A conduction during magnet application (fixed rate pacing)	0–6*
Competing atrial rhythm during normal pacemaker function	0–2*
Score	0–50

*Assessed by assisting senior cardiac technician.
JVP, jugular venous pulse. V-A, ventriculoatrial.
Clinical examination included evaluation of: pacemaker dependency*; concurrent medication; pulse rate, character and rhythm; blood pressure; jugular venous pulse wave level and character; myopotential inhibition*; arrhythmia type and duration.*

OBJECTIVE ASSESSMENT

(i) *Graded exercise treadmill testing*

Patients were monitored by a continuous six-lead electrocardiogram and were assessed by the Chronotropic Assessment Exercise Protocol (CAEP).[14] Tests were symptom limited and the decision to stop the protocol was made by the supervising clinician alone. A senior cardiac technician monitored the electrocardiogram during all tests. Total exercise time and resting and peak heart rates were obtained for each patient.

(ii) *Staircase ascent*

Patients had their heart rates measured by telemetry using a Hewlett Packard 78571B ECG recorder while they climbed as many stairs as they could to a maximum of five flights (each comprising fifteen steps, 15 cm tall, pitch 27 cm), as fast as possible. Heart rate was assessed at rest before the ascent and every 15 seconds for two minutes. The number of stairs ascended and the percentage change in heart rate were calculated.

RADIOLOGICAL ASSESSMENT

Chest radiographs were obtained 24 hours before the upgrading procedure, 24 hours postoperatively with the patient programmed to VVI mode, and finally after a four week study period programmed to a dual chamber mode (either DDI or DDD) chosen randomly by the assisting senior technician. These were designated as "VVI pre", "VVI post", and "Dual" radiographs respectively.

After completion of the study radiographs were independently analysed by two clinicians who were unaware of the patient's name, the pacing mode, or dates of the radiographs. The cardiothoracic ratio was calculated as the widest dimension of the cardiac shadow (in centimetres) divided by the widest internal dimension of the thoracic cage (in cm) and expressed as a percentage. An arbitrary "pulmonary oedema severity score" was devised where: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

ECHOCARDIOGRAPHIC ASSESSMENT

A Hewlett-Packard 77020A system with a 2·5 MHz duplex probe and a 1·9 MHz continuous wave transducer was used. Serial studies on individual subjects were carried out by the same operator to avoid inter-observer variability.

M-mode recordings were taken at conventional levels with dimensions estimated from leading edge to leading edge.[15] To ensure that the operator remained "blinded" to the pacing mode simultaneous electrocardiographic recording was not used. This meant that the left ventricular diastolic diameter was taken as the greatest dimension in diastole and the systolic diameter as the smallest dimension in systole.

Stroke volume was calculated as the product of the systolic velocity integral and cross sectional area for flow by a combined cross sectional Doppler technique. Subaortic cross-sectional area was measured from inner to inner echo at the level of the annulus in a parasternal long axis frame frozen early in systole.[16] The systolic velocity integral was calculated from the aortic envelope recorded from the apical position. This was averaged over five beats by triangulation (stroke volume index (SVI) = 1/2 × ejection time × V_{max}). This has been shown to be equivalent to planimetry.[17 18]

Pulmonary artery systolic pressure was estimated where possible from the peak velocity of the tricuspid regurgitant jet recorded by continuous wave Doppler. Pressure (p) was calculated by the formula of Berger *et al*[19] where $p = 6/5 \times 4(V_{max})^2$. Signals lacking a clearly defined envelope were discarded.

The colour flow Doppler system was set to the same enhanced threshold map for every study with maximum packet size, minimum reject, and spatial filtering. The gain was set to the level just below that at which colour flooding occurred. Mitral and tricuspid regurgitant jets were measured by planimetry in the view that gave the largest jet area, and the results were expressed as a percentage of the total right or left atrial area.[20 21]

STATISTICAL ANALYSIS

All results are reported as mean (SD). Non-parametric data arising from subjective questionnaires, visual analogue scales, and the clinical assessment score were compared by the Wilcoxon signed rank test while parametric data arising from objective tests were compared by Student's paired *t* test. Student's unpaired *t* tests were used for inter-patient subgroup comparisons. If more than two comparisons were undertaken of a given variable the Bonferroni correction was used. A p value of less than 0·05 was regarded as significant.

Results

SUBJECTIVE ASSESSMENT

Figure 1 shows the patients' perception of "general well-being" and exercise capacity. General well-being was significantly better in DDD mode than in either VVI pre mode or VVI post mode, (p < 0·01). Perceived exercise capacity was similar in VVI pre, VVI post, and DDI modes but was significantly greater in DDD mode (p < 0·01).

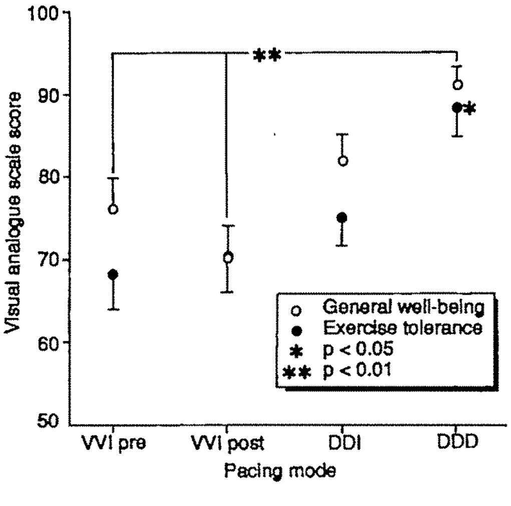


Figure 1 Perceived general well-being and exercise capacity in the study pacing modes (see text for details).

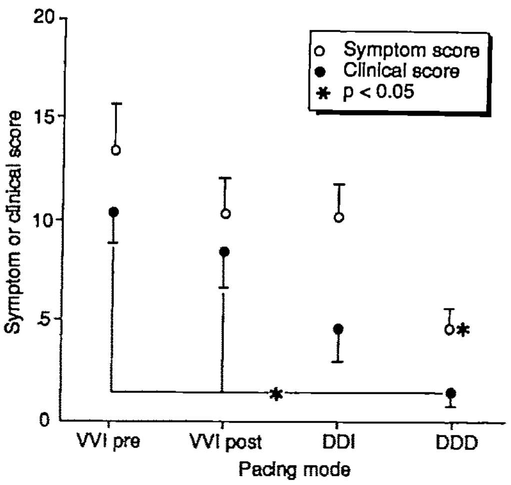


Figure 2 Symptom prevalence score and clinical assessment score in the four study pacing modes.

There was no significant difference in perceived functional status in any mode throughout the study. However, specific symptom scores were significantly lower (that is, fewer symptoms) in DDD mode than in the remaining study modes (p < 0·05, fig 2).

Figure 3 shows the overall preferred and least acceptable modes which were selected after the end of the study. There was good correlation with the preferences indicated in the subjective questionnaires. VVI was not selected as an outright preferred mode by any patient. Sixty nine per cent selected DDD, one patient selected DDD or VVI pre (6%), 12% DDI (one of the two patients had paroxysmal supraventricular arrhythmias), and 12% had no preference. No patient selected DDD as their least acceptable mode. However, two patients (12%) found the DDI mode least acceptable. Both these patients had been randomised initially to the VVI post mode and then to DDD before being programmed to the DDI mode. The VVI pre mode was the least acceptable to three patients (18%) while the VVI post mode was least acceptable to 50% of patients. The two patients who had no preference for any mode were not pacemaker dependent.

Three patients demanded early crossover to the next programmed mode during the study. One patient initially randomised to DDD mode after the pacemaker was upgraded could not tolerate either DDI or VVI modes thereafter. The remaining two patients had been randomised to DDD mode before VVI mode and found the latter intolerable. (One of these patients did not request early reprogramming from the DDI mode which followed VVI mode).

CLINICAL EXAMINATION

The clinical assessment score was significantly greater (that is, there were more signs of pacemaker syndrome) in both VVI modes than

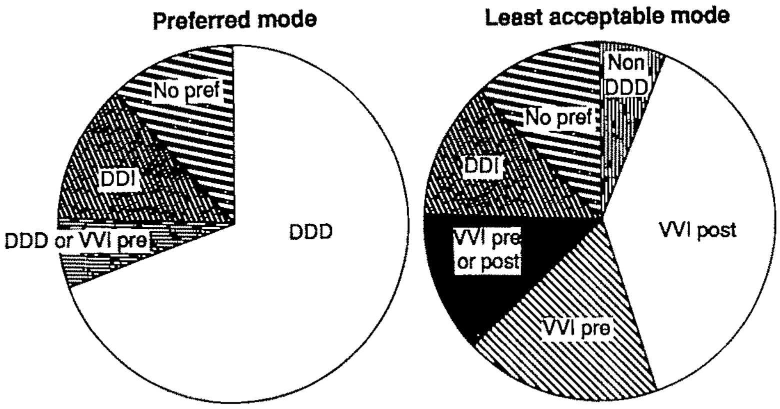
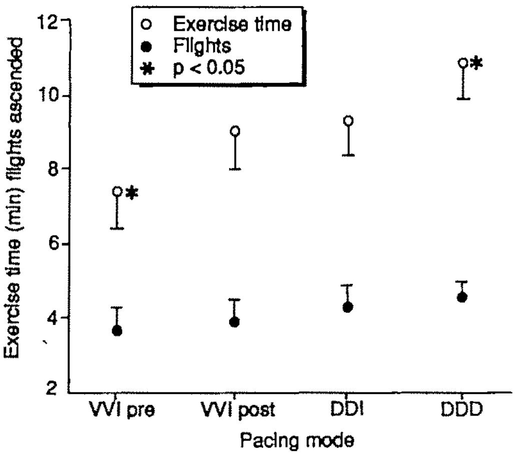


Figure 3 Preferred and least acceptable pacing modes defined by patients after completion of the study.

Figure 4 Objective study indices: exercise time while undertaking the CAEP exercise treadmill test and during staircase ascent (see text for details).



in the DDD mode ($p < 0{\cdot}05$), but did not differ from that in the DDI mode (fig 2). Mean arterial blood pressure measured at rest during clinical assessment did not significantly differ in any mode (VVI pre 103·6 (4·0) mm Hg, VVI post 103·2 (3·0) mm Hg; DDI 107·9 (3·4) mm Hg; DDD 107·3 (3·0) mm Hg).

OBJECTIVE ASSESSMENT

(i) *Graded exercise treadmill tests (fig 4)*
Exercise times were longer in dual modes, but there were no significant differences between any modes except VVI pre mode and DDD (7·4 (1·0) min and 10·9 (1·0) min respectively, $p < 0{\cdot}05$) during the CAEP protocol.

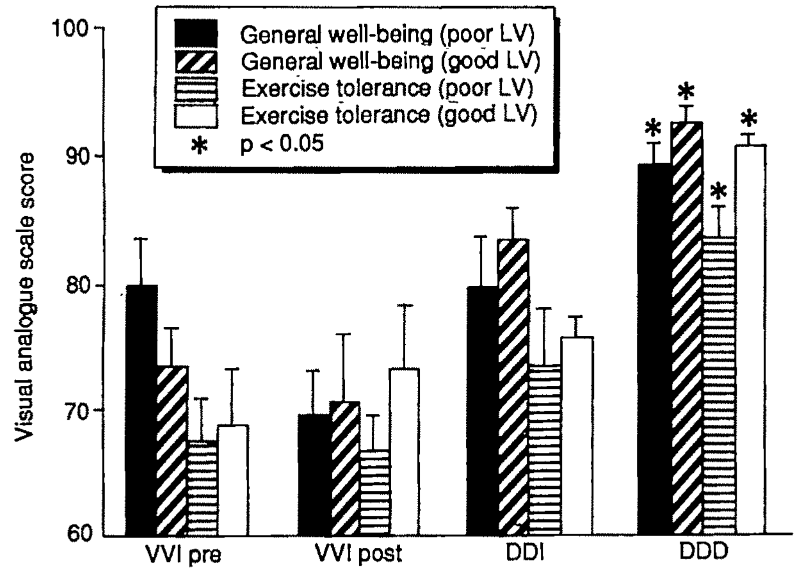


Figure 5 Perception of general well-being (GW) and exercise capability (ET) according to left ventricular systolic function. Poor LV, left ventricular shortening ≤ 25%; good LV, left ventricular shortening > 25%.

(ii) *Staircase ascent (fig 4)*
The mean number of stairs ascended was greater in dual modes than in the VVI pre or VVI post modes, but this difference did not reach statistical significance (3·7 (0·4) flights, in VVI pre mode; 3·9 (0·4) flights in VVI post; 4·3 (0·4) flights in DDI mode, and 4·6 (0·2) flights in DDD mode). The percentage change in heart rate during both of the above protocols was significantly greater in DDD than in the remaining modes, which did not significantly differ (CAEP treadmill test expressed as a percentage change in heart rate from rest to peak exercise in VVI pre 10·7 (6·7), VVI post 16·6 (9·5); DDI 14·9 (6·0) (p = NS), DDD mode 59·6 (7·8) ($p = 0{\cdot}001$); staircase ascent expressed as percentage change in heart rate from rest to peak rate in VVI pre 12 (6·3), VVI post 10·9 (5·7); DDI 14·6 (6·8) (p = NS), DDD 46·5 (7·7) ($p < 0{\cdot}001$).

Patient data were divided into two subgroups according to left ventricular systolic function assessed by echocardiography. ("Good LV" indicated fractional shortening greater than 25% and "poor LV" fractional shortening 25% or less (table 1)).

Left ventricular function had no influence on the significant effects shown in the different modes on any variables discussed above (fig 5) except for exercise treadmill testing when the previously detected significant increase in exercise tolerance in DDD mode is no longer evident in either the "good" or "poor" left ventricle groups ($p = 0{\cdot}09$ and $p = 0{\cdot}065$ respectively with Bonferroni correction).

RADIOLOGICAL ASSESSMENT

There was no significant difference in the cardiothoracic ratio at any stage of the study; (VVI pre, 49·5 (1·1)%; VVI post, 51·2 (1·3)%; dual, 50·75 (1·4)% (p = NS)). The incidence of pulmonary oedema was similar in all stages of the study (18% in VVI pre and 24% in both VVI post and dual. The arbitrary pulmonary oedema severity scores in these patients were 1·7 (0·6), 1·5 (0·6), and 1·0 (0·3), respectively (p = NS).

ECHOCARDIOGRAPHIC ASSESSMENT

Cardiac dimensions did not differ in any mode during the study. Left ventricular fractional shortening was similar in all modes (VVI pre, 27·9 (2·8)%; VVI post, 27·1 (2·4)%; DDI, 26·7 (2·8)%; and DDD, 25·5 (2·5)% (p = NS)). Pulmonary arterial pressure was evaluable in all modes in only eight patients (50%). In this cohort there was no significant difference in pulmonary artery pressure in any mode.

The incidence of mitral and tricuspid regurgitation was less in the DDD mode but this did not reach statistical significance (Mitral regurgitation: VVI pre, 50%; VVI post, 63%; DDI, 63%; and DDD, 30%. Tricuspid regurgitation: VVI pre, 63%; VVI post, 63%; DDI, 63% and DDD, 50%). However, the extent of the regurgitant jets assessed by colour

Figure 6 Extent of mitral and tricuspid regurgitation detected by colour flow Doppler echocardiography in the study pacing modes.

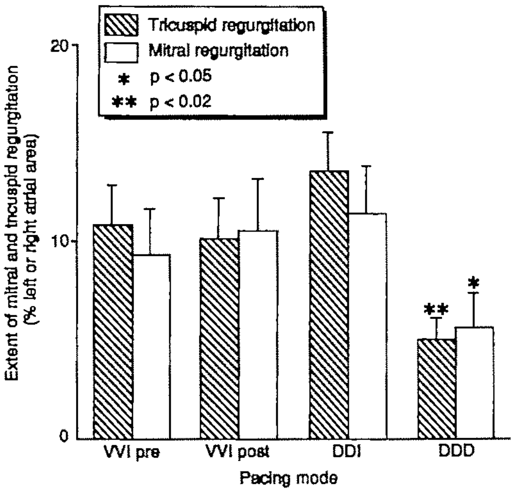
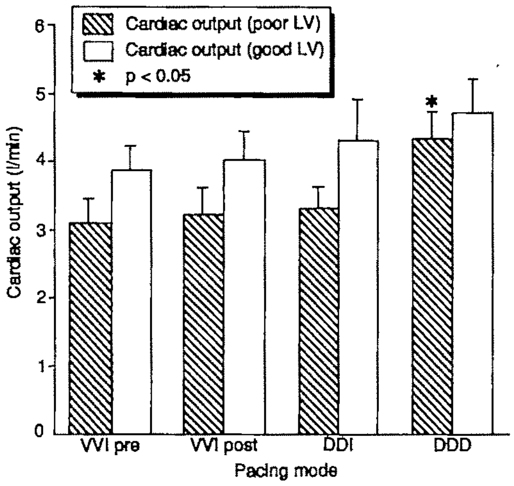


Figure 7 Cardiac output in each study pacing mode categorised according to patients' left ventricular systolic function.



flow Doppler was significantly less in the DDD mode than in the remaining modes (fig 6).

Cardiac output was least in the single chamber modes and greatest in the DDD mode but these values were not statistically significant (cardiac output in VVI pre, 3·6 (0·3) l/min, in VVI post, 3·6 (0·4) l/min, in DDI 3·8 (0·4) l/min; in DDD mode 4·5 (0·3) l/min ($p = 0{\cdot}065$).

Echocardiographic data reanalysed with patients sub-divided according to left ventricular function showed no differences from combined data with the sole exception of cardiac output. In the subgroup with poor left ventricular function cardiac output was significantly greater in DDD mode (4·3 (0·4) l/min than in the remaining modes (VVI pre, 3·1 (0·4) l/min, VVI post 3·2 (0·4) l/min, DDI 3·3 (0·3) l/min ($p = 0{\cdot}03$)). This was not evident in the subgroup with good left ventricular function (cardiac output in DDD mode, 4·7 (0·3) l/min; VVI pre, 3·9 (0·25) l/min; VVI post, 4·0 (0·3) l/min; DDI, 4·3 (0·4) l/min (p = NS), fig 7).

Discussion

The advantages of physiological, atrioventricular sequential pacing are now widely accepted with several studies showing improvement in objective and subjective indices in dual modes compared with VVI mode.[4 22-24] In addition, patient characteristics do not allow identification of those at risk from the pacemaker syndrome before pacemaker implantation. It occurs at any age, in both sexes, as often in patients with morphologically normal hearts as in those with cardiac disease, with or without ventriculoatrial retrograde conduction, and it may occur at any time during ventricular demand pacing.[1 2 3 25 26] Moreover VVI pacing, especially for sinus node disease, may adversely affect long-term prognosis.[9 27] Nevertheless VVI pacemakers are the most commonly used devices for all indications for permanent pacing worldwide.[27]

MODE PREFERENCE

This study provides evidence that when patients without the overt symptoms of the pacemaker syndrome (most VVI paced patients) are upgraded to dual chamber synchronous (DDD) pacing they show a considerable improvement in subjective and objective indices.

Mitsuoka *et al* found similar subjective benefit in patients paced with dual chamber devices for sick sinus syndrome, but many of these patients had retrograde ventriculoatrial conduction and overt signs of the pacemaker syndrome when paced in the VVI mode.[28]

These findings may result from the effects of the rate response offered by DDD mode but lacking in the remaining study modes except in the non-pacemaker dependent patients. However, subjective indices were worse in the VVIR mode than in the DDDR mode in patients with chronotropic incompetence—so that it seems that atrioventricular synchrony is a major factor resulting in improved patient acceptability.[29]

In the present study, the choice of least acceptable mode was highly dependent upon the programming sequence. Hence if VVI post was the first postoperative mode programmed, subjective scores were better than if the VVI post mode followed the DDD mode. The same was true for DDI and could explain why it was selected as the least acceptable mode by two patients and caused a request for early reprogramming in one case. (In both patients the VVI post mode was programmed before the DDD mode and the DDI mode was programmed after the DDD mode. Mode sequence had little effect on objective study indices, however. The DDI mode was little different from the VVI mode in most patients. This may be due to the lack of rate response in either mode although increased rate responsive pacing is required for less than 15% of the day during out of hospital activity.[30] Because most of the day is spent at low heart rates, when dual chamber synchronous pacing occurs in DDI mode (with the "atrial kick" exerting its most beneficial effects[31]) in theory this mode should be haemodynamically better than the VVI mode and hence more acceptable to the patient. The most prevalent symptom in the DDI mode was "palpitations" (rather than "tiredness" in the VVI mode) and this may have been caused by loss of atrial synchrony on mild exertion as the atrial rate increased and the pacemaker, in effect, defaulted to VVI pacing. This persistent "mode switching" may be the feature that is least acceptable to most patients, and thus the DDI mode should be used only in selected patients with paroxysmal arrhythmias.[32]

There was a small, non-significant increase in perceived exercise capacity and a decrease in symptom prevalence in the VVI post mode compared with the VVI pre mode. This is likely to be a placebo response resulting from the implantation of a more sophisticated device.

OBJECTIVE STUDY INDICES

Nishimura and colleagues showed considerable falls in mean arterial blood pressure in patients with pacemaker syndrome that resolved with dual chamber pacing.[3] We did not show any significant differences in any mode, probably because none of our patients had overt pacemaker syndrome.

Treadmill tests, but not staircase ascent, showed a significant increase in exercise tolerance in DDD mode compared with the VVI pre mode as has previously been shown.[4 23] However, the staircase ascent did not exercise all patients to their maximum tolerance and thus differences were less well demarcated during this "everyday activity" stress protocol.

Exercise tolerance was greater in the VVI post mode than in the VVI pre mode (although not significantly so), partly because of a placebo response (most subjects might have expected some improvement in exercise capability after the upgrading). There might also be a training effect between these modes, despite familiarisation with the treadmill before study induction and the randomisation of postoperative pacing modes, as all patients necessarily performed at least one more treadmill protocol in the VVI post mode than in the VVI pre mode.

Reanalysis of data according to echocardiographically derived left ventricular fractional shortening and not the ejection fraction was based on the findings of Gomes *et al* who showed that the asymmetry of ventricular depolarisation induced by right ventricular apical pacing causes significant errors in the estimation of ejection fraction.[33]

Stewart *et al* using similar techniques showed that the increase in cardiac output between VVI and DDD modes was greatest in patients with the most overt symptoms of the pacemaker syndrome when paced in VVI mode.[34] Interestingly, although there was an increased cardiac output detected in the DDD mode compared with the remaining modes this did not reach statistical significance in our study population. Thus it seems that patients who tolerate VVI pacing well have a less considerable haemodynamic benefit from dual chamber pacing at rest despite clear subjective improvement during everyday activity.

In the subgroup with poor left ventricular function, however, there was a significant increase in cardiac output at rest confirming the findings of Pearson *et al.*[35] Although these patients showed more haemodynamic benefit in terms of cardiac output, subjective scores were similarly favourable to DDD mode in both the subgroups. This suggests that the improved symptoms and general health perception is largely independent of left ventricular systolic function. Similar findings with rate responsive pacing modes confirm that improved cardiac output is not the sole factor in patient preference for atrioventricular sequential pacing.[29]

Both echocardiography and chest radiology confirmed that the cardiac dimensions did not vary during long-term pacing in any study mode. This is contrary to findings in patients with overt pacemaker syndrome, where heart failure on chest radiography (and clinically) was more often seen in the VVI than in the DDD mode.[1 22]

Although the incidence of both mitral and tricuspid regurgitation was similar in all modes, the extent of both mitral and tricuspid regurgitation was significantly less in DDD mode and was independent of left ventricular function. Valve incompetence has been proposed as a cause of the pacemaker syndrome,[36] and the extent of valve regurgitation, but not the incidence, may be a factor in the genesis of "subclinical" pacemaker syndrome.

Only four of 14 patients assessed in the present study had consistent retrograde ventriculoatrial conduction and the small size of this subgroup precludes meaningful statistical analysis. Rediker *et al* have recently identified patients with an increase in systolic blood pressure from VVI to DDD pacing and with ventriculoatrial conduction who benefited most from dual chamber pacing.[37] These findings suggest that our study population was free from the pacemaker syndrome and unlikely to benefit from DDD pacing. Despite this, most patients preferred the DDD mode and found the VVI mode least acceptable after completion of the study. Retrospective analysis of data to predict maximum benefit from dual chamber pacing in symptom free VVI paced patients was inappropriate because of disparate sample sizes. Larger patient numbers might allow such analysis.

CLINICAL IMPLICATIONS

Few studies have compared VVI and DDD with DDI mode pacing. Although patient numbers in this study were small, with each acting as their own control, the results suggest that DDI mode is subjectively and objectively similar to the VVI mode and not as good as the DDD mode. The DDI mode should therefore be used only in patients who cannot tolerate DDD pacing (because of frequent paroxysmal atrial arrhythmias).

Our data suggest that "subclinical" pacemaker syndrome occurs in nearly three quarters of symptom free VVI paced patients. Combined with the incidence of overt pacemaker syndrome in up to 20% of patients with VVI devices,[1] 80% of all VVI paced patients without atrial fibrillation would benefit from DDD pacing, and this effect persists even after long-term VVI mode pacing.

Comparable findings were seen in the VVIR mode when it was compared with dual chamber rate responsive modes,[29] which suggests that a similar "subclinical" pacemaker syndrome may exist with this pacing mode. (It is well known that VVIR mode can cause severe pacemaker syndrome.[38])

Hence, VVI pacing should be used only in patients with chronic or persistent atrial fibrillation with good chronotropic response to exercise, or with transient bradycardic arrhythmias. This investigation confirms the adage: If there is a P wave available, sense it and synchronously pace the ventricle if necessary.

We thank Miss Lynne Chappell for typing the paper.

1 Ausubel K, Furman S. The pacemaker syndrome. *Ann Intern Med* 1985;103:420–9.

2 Alicandri C, Fouad FM, Tarazi RC, Castle L, Morant V. Three cases of hypotension and syncope with ventricular pacing: possible role of atrial reflexes. *Am J Cardiol* 1978;42:137–42.

3 Nishimura RA, Gersh BJ, Vlietstra RE, *et al*. Hemodynamic and symptomatic consequences of ventricular pacing. *PACE* 1982;5:903–10.

4 Perrins EJ, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. *Br Heart J* 1983;50:112–7.

5 Nishimura RA, Gersh BJ, Holmes DR, *et al*. Outcome of dual chamber pacing for the pacemaker syndrome. *Mayo Clin Proc* 1983;58:452–6.

6 Torresani J, Bogosti A, Allard-Latour P, *et al*. Pacemaker syndrome with DDD pacing. *PACE* 1984;7:1148–51.

7 Cunningham TM. Pacemaker syndrome due to retrograde conduction in a DDI pacemaker. *Am Heart J* 1988; 115:478–9.

8 Barold SS, Mugica J, eds. *The third decade of cardiac pacing: advances in technology and clinical applications*. New York: Futura Publishing Co, 1982:22–42.

9 Rosenqvist M. Atrial pacing for sick sinus syndrome. *Clin Cardiol* 1990;13:43–7.

10 Camm AJ, Butrous GS. Clinical cardiac electrophysiology. In: Julian DG, Camm AJ, Fox KM, *et al*, eds. *Diseases of the heart*. London: Balliere Tindall, 1989:233–53.

11 Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analog scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56.

12 Von Olshausen KE, for the German and Austrian xamoterol study group. Double-blind placebo-controlled comparison of digoxin & xamoterol in chronic heart failure. *Lancet* 1988;i:489–93.

13 Goldman L, Hashimoto B, Cook F, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activities scale. *Circulation* 1981;64:1227–34.

14 Wilkoff BL, Corey J, Blackburn G. A mathematical model of the cardiac chronotropic response to exercise. *J Electrophysiol* 1989;3:176–80.

15 Sahn D, DeMaria AN, Kisslo J, Wetman A. Recommendations regarding quantitation in M mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–83.

16 Magnin PA, Stewart JA, Myers S, *et al*. Combined Doppler and phased-array echocardiography estimation of cardiac output. *Circulation* 1981;63:388–92.

17 Chandraratna PA, Nanna M, McKay C, *et al*. Determination of cardiac output by transcutaneous continuous wave ultrasonic Doppler computer. *Am J Cardiol* 1984;53: 234–57.

18 Haites NE, McLennan FM, Mowat DHR, Rawles JM. Assessment of cardiac output by the Doppler ultrasound technique alone. *Br Heart J* 1985;53:123–9.

19 Berger M, Haimowitz A, Van Tosh A, *et al*. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985;6:359–65.

20 Chopra HK, Nanda NC, Fan P, *et al*. Can two dimensional echocardiography and Doppler color flow mapping identify the need for tricuspid valve repair? *J Am Coll Cardiol* 1989;14:166–74.

21 Helmcke F, Nanda NC, Hsiung MC, *et al*. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;75:175–83.

22 Kruse IB, Arnman K, Conradson TB, Ryden L. A comparison of the acute and long-term effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1982;65:846–55.

23 Kristensson B-E, Arnman K, Ryden L. The haemodynamic importance of atrioventricular synchrony and rate increase at rest and during exercise. *Eur Heart J* 1985;6:773–81.

24 Haas JM, Strait GB. Pacemaker-induced cardiovascular failure. Hemodynamic and angiographic observations. *Am J Cardiol* 1974;33:295–9.

25 Furman S. Cardiac pacing and pacemakers. VI. Analysis of pacemaker malfunction. *Am Heart J* 1977;94:378–86.

26 Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;116:16–22.

27 Tyers FO. Current status of sensor modulated rate adaptive cardiac pacing. *J Am Coll Cardiol* 1990;15:412–8.

28 Mitsuoka T, Kenny RA, Yeung TA, Chan SL, Perrins JE, Sutton R. Benefits of dual chamber pacing in sick sinus syndrome. *Br Heart J* 1988;60:338–47.

29 Sulke AN, Chambers JB, Dritsas A, Sowton E. A randomised double blind crossover study of four rate responsive pacing modes. *J Am Coll Cardiol* 1991;17: 696–706.

30 Sulke AN, Pipilis A, Bucknall CA, Sowton E. Quantitative analysis of contribution of rate response in three different VVIR pacemakers during out of hospital activity. *PACE* 1990;13:37–44.

31 Karlof I. Hemodynamic effects of atrial triggered versus fixed rate pacing at rest and during exercise in complete heart block. *Acta Med Scand* 1975;197:195–206.

32 Bana G, Locatelli V, Piatti L, *et al*. DDI pacing in bradycardia-tachycardia syndrome. *PACE* 1990;13: 264–70.

33 Gomes JAC, Damato AN, Akhtar M, *et al*. Ventricular septal motion and left ventricular dimensions during abnormal ventricular activation. *Am J Cardiol* 1977; 39:641–5.

34 Stewart WJ, Dicola VC, Harthorne JW, *et al*. Doppler ultrasound measurement of cardiac output in patients with physiologic pacemakers. *Am J Cardiol* 1984;54:308–12.

35 Pearson AC, Janosik DL, Redd RM, *et al*. Hemodynamic benefit of atrioventricular synchrony: predication from baseline Doppler echocardiographic variables. *J Am Coll Cardiol* 1989;13:1613–21.

36 Naito M, Dreifus LS, Mardelli TJ, *et al*. Echocardiographic features of atrioventricular and ventriculoatrial conduction. *Am J Cardiol* 1980;46:625–33.

37 Rediker DE, Eagle KA, Homma S, *et al*. Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. *Am J Cardiol* 1988; 61:323–9.

38 Liebert HP, O'Donoghue S, Tullner WF, *et al*. Pacemaker syndrome in activity responsive VVIR pacing. *Am J Cardiol* 1989;64:124–6.

Br Heart J 1992;**67**:65–6

Pacemaker electrode implantation in patients with persistent left superior vena cava

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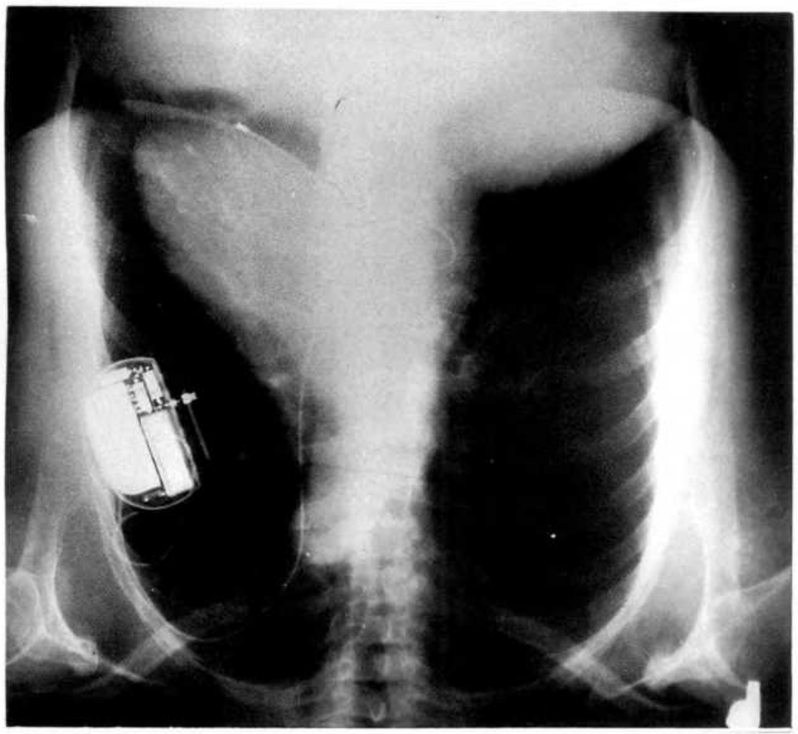
Abstract

Four out of 661 consecutive patients with permanent endocardial VVI pacing had the pacing lead introduced through a persistent left superior vena cava. It was difficult to introduce the lead from the right atrium into the right ventricle because the tip of the lead tended to be deflected away from the tricuspid orifice. This difficulty was overcome by shaping the lead into a pigtail with 3–4 cm wide loop. This avoided the risk of entering a branch of the coronary sinus in order to reach the right atrium.

This technique made it easier to position the lead in the right ventricular apex. There were no complications in these four patients during a mean follow up of three years.

Placement of pacemaker electrodes can be complicated by congenital anomalies of the systemic superior veins, including a persistent left superior vena cava with normal right superior vena cava (a double system), a single left superior vena cava, and absence of drainage by a superior vena cava.[1]

A persistent left superior vena cava arises from the confluence of the left jugular and subclavian veins and passes down to enter the right atrium through the coronary sinus. Such an arrangement is seldom recognised on the plain chest x ray but because of the unusual course of a lead (figure) it becomes obvious on the screen when a pacemaker lead is being introduced. Once the right atrium is reached through the coronary sinus further placement of a lead in the right ventricle can be difficult because the tip of the lead is deflected away from the tricuspid orifice.



Course of the pacemaker lead introduced through persistent left superior vena cava in patient 4.

Patients and methods

Among 661 patients who had permanent unipolar pacemaker (VVI) leads inserted from a branch of the left subclavian vein between January 1982 and July 1990 there were four patients in whom the pacemaker lead was introduced through the persistent left superior vena cava (table). In all four the unusual left-sided downward course taken by the electrode lead during the procedure alerted us to the presence of a persistent left superior vena cava. We found that if we reshaped the end of the stylet into the pigtail configuration we were able to place the lead in the right ventricle without difficulty.

In three of the four patients we also had to change to a curved stylet before the tip of the lead could be positioned in the right ventricular apex. During a mean follow up of 35·2 months there were no complications.

Discussion

During fetal life the superior vena cava develops from the right anterior and common cardinal veins. The left anterior cardinal vein becomes the proximal parts of the left internal jugular and subclavian veins draining through the anastomotic channel (left brachiocephalic vein) into the superior vena cava. The left common cardinal vein and distal left sinus horn become the left superior vena cava (draining to the coronary sinus) which normally regresses, its site being marked by the oblique ligament and vein of Marshall. If this process is interrupted a double caval system develops. Other much rarer anomalies that can affect pacemaker lead insertion include single left persistent vena cava or even the complete lack of superior caval drainage.[1] Such anomalies are seldom found without other congenital defects. For instance, the estimated incidence of a double superior caval system in the general population is 0·1%–0·5%.[2 3]

Anomalies of the superior caval system can

Details of patients with pacemaker leads implanted through a persistent left superior vena cava

Patient	Age at implantation, sex	Indication for pacing	Follow up (mnth)*	Outcome
1	63, F	2° AV block	22	Lost to follow up
2	73, M	3° AV block	49	Alive
3	76, F	2° AV block	16	Died, cause unknown
4	55, F	SSS (sinus bradycardia)	54	Alive

*Mean 35·2 months.
AV, atrioventricular; SSS, sick sinus syndrome.

be diagnosed by conventional angiography, by cross sectional echocardiography combined with peripheral venous injection of contrast medium,[4] by intravenous digital subtraction angiography,[5] by radionuclide angiography,[6] and by magnetic resonance imaging.[7]

Attempts to define the anatomy of the superior caval system before pacemaker implantation are not routine because anomalies are rare and because the most commonly encountered anomaly, a persistent left superior vena cava, does not preclude successful lead placement.

Many isolated cases have been reported and Trigano reviewed 39 cases.[3] Experience indicates that it is possible to introduce a pacemaker lead into the right ventricle for effective pacing in one chamber pacing[8-10] and dual chamber pacing[11-13] and into the right atrium for atrial pacing.[14]

When the pacemaker lead enters the right atrium through the persistent left superior vena cava and the coronary sinus it often forms a loop in the right atrium and then enters the right ventricle. Rarely a lead may reach the right ventricle without forming a loop or enter a branch of the coronary sinus; these two courses are sometimes difficult to distinguish in the anterior-posterior view.[3] Fortunately, ventricular pacing (usually from a branch of the coronary sinus) and atrial pacing (from the distal coronary sinus)[15 16] seem to be safe long term procedures. Appropriate curving of a stylet, for instance into a pigtail loop 3–4 cm wide but without complete "closing" of a loop, as in our cases, facilitated insertion of a lead to the right ventricle by directing the lead into the tricuspid orifice.

It is important to know the technique of implanting a pacing lead through the persistent left superior vena cava because in patients with a single left superior vena cava the only alternative is the transthoracic approach with all its inherent risks. The transthoracic approach seems to be mandatory only in those very rare cases of a single persistent left superior vena cava draining to the left atrium.[17] Such a case has not been so far described in connection with pacemaker lead implantation. There is no need to use active fixation leads with screw-in or pinch-in tips.

1 Amjad Hussein S, Chakravarty S, Chaikhouni A, Smith JR. Congenital absence of superior vena cava: unusual anomaly of superior systemic vein complicating pacemaker placement. *PACE* 1981;4:328–32.

2 Steinberg I, Dubilier W, Lukas D. Persistence of left superior vena cava. *Dis Chest* 1953;24:479–82.

3 Trigano JA. Permanent pacing through a persistent left superior vena cava in 39 collected cases. *Clin Prog Electrophysiol Pacing* 1986;4:45–52.

4 Foale R, Bourdillon PD, Somerville J, Rickards A. Anomalous systemic venous return: recognition by two-dimensional echocardiography. *Eur Heart J* 1983;4:186–95.

5 Yiannikas J, Moodie DS, Gill CC, Sterba R, McIntyre R, Buonocore E. Intravenous digital subtraction angiography in the assessment of patients with left to right shunts before and after surgical correction. *J Am Coll Cardiol* 1984;3:1507–14.

6 Otto AC, Answegen A, Herbst CP, *et al*. Persistent left superior vena cava detected with radionuclide angiocardiography. *Clin Nucl Med* 1985;10:27–9.

7 Fisher MR, Hricak H, Higgins CB. Magnetic resonance imaging of developmental venous anomalies. *Am J Roentgenol* 1985;145:705–9.

8 Rose ME, Gross L, Protos A. Transvenous pacemaker implantation by way of an anomalous left superior vena cava. *J Thorac Cardiovasc Surg* 1971;62:965–6.

9 Harris A, Gialafos J, Jefferson K. Transvenous pacing in presence of anomalous venous return to heart. *Br Heart J* 1972;34:1189–91.

10 Gillmer DJ, Vyhilingum S, Mitha AS. Problems encountered during insertion of permanent endocardial pacing electrode. *PACE* 1981;4:212–5.

11 Westerman GR, Baker J, Dungan WT, Van Devanter SH. Permanent pacing through a persistent superior vena cava: an approach and report of dual-chambered lead placement. *Ann Thorac Surg* 1985;39:174–6.

12 Zardo F, Nicolosi GL, Burelli C, Zanuttini D. Dual-chamber transvenous pacemaker implantation via anomalous left superior vena cava. *Am Heart J* 1986;112;621–2.

13 Dirix LY, Kersschot IE, Fierens H, Goethals MA, Van Daele G, Claessen G. Implantation of a dual-chamber pacemaker in a patient with persistent left superior vena cava. *PACE* 1988;11:343–5.

14 Robbens EJ, Ruiter JH. Atrial pacing via unilateral persistent left superior vena cava. *PACE* 1986;9:594–6.

15 Moss AJ, Rivers RJ, Cooper M. Long-term pervenous atrial pacing from the proximal portion of the coronary vein. *JAMA* 1969;209:543–5.

16 Greenberg P, Castellanet M, Messenger J, Ellestad MH. Coronary sinus pacing. *Circulation* 1978;57:98–103.

17 Wiles HB. Two cases of left superior vena cava draining directly to a left atrium with a normal coronary sinus. *Br Heart J* 1991;65:158–60.

Br Heart J 1992;67:67–71

Catheter ablation by low energy DC shocks for successful management of atrial flutter

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Abstract

***Objective*—To assess the effects of low energy ablation of the substrate for atrial flutter.**

***Design*—Initial retrospective analysis of patients undergoing low energy ablation of the atrioventricular node for refractory atrial flutter (group 1) was followed by a prospective assessment of low energy ablation in the posterio-inferior right atrium for the same condition (group 2).**

***Setting*—Tertiary referral centre for management of cardiac arrhythmias.**

***Patients*—Seven men (aged 50–67 years) with refractory atrial flutter.**

***Interventions*—Multiple (3–10) low energy DC shocks with a cumulative energy of 100-245 J in the region of the atrioventricular node in group 1 and 12–15 low energy DC shocks (cumulative energy 110–235 J) guided by the anatomical landmarks of the triangle of Koch and applied directly to the atrial wall.**

***Main outcome measure*—Freedom from recurrence of atrial flutter.**

***Results*—In group 1 despite initial complete atrioventricular block in three patients, atrioventricular conduction had resumed in all by one month. All four, however, were in sinus rhythm at follow up six to 13 months later. Two of the three patients in group 2 were free of atrial flutter at follow up three to four months after ablation.**

***Conclusion*—Ablation of the atrial flutter substrate with low energy DC shocks is feasible. Precise electrophysiological mapping is not necessary.**

Atrial flutter is a common arrhythmia for which no entirely satisfactory treatment is available. Though DC cardioversion is often successful in restoring sinus rhythm in the short term, relapses are common. Despite the growing number of pharmacological agents available for arrhythmia prophylaxis many patients are either intolerant of drug treatment or achieve inadequate relief from their symptoms. In this group atrioventricular node/His bundle ablation has been the treatment of choice. This is not an ideal solution, however, because it requires the insertion of a permanent pacemaker, the atrial arrhythmia is not abolished, and the procedure itself has a small but significant morbidity and mortality.[1 2]

A more attractive approach to the long term management of atrial flutter has been to tackle the arrhythmia substrate directly.[3–5] This has been made possible by the improved understanding of the mechanisms of flutter gained from animal models of the arrhythmia and from human intracardiac electrophysiology studies.[6–8] It seems from such studies that the typical form of atrial flutter is due to a macroreentry circuit within the right atrium with an area of slow conduction posterio-inferiorly in the triangle of Koch, between the os of the coronary sinus and the atrioventricular valve ring. Cryoablation of this area, guided by intraoperative epicardial mapping, has been successfully used to prevent recurrence of the arrhythmia.[3] More recently high energy endocardial DC ablation has been performed guided by endocardial mapping techniques. We have used low energy DC shocks for endocardial ablation because high energy discharges have been shown to cause significant barotrauma to cardiac structures remote from the intended site of injury. We achieved long term remission of atrial flutter in four patients with chronic atrial flutter in whom the aim of the procedure had been to achieve atrioventricular block. This serendipitous abolition of atrial flutter suggested to us that precise mapping of the area of slow conduction was not necessary for successful ablation of the atrial flutter circuit. We therefore prospectively used multiple low energy shocks guided by the anatomical landmarks of the triangle of Koch in an attempt to abolish the arrhythmia substrate.

Patients and methods

PATIENTS

We studied seven men (age 50–67 years) with either chronic or paroxysmal atrial flutter that was refractory to medical treatment (table 1). All had severe symptoms from their arrhythmia; during exercise three patients had experienced pre-syncope caused by 1:1 conduction of the arrhythmia to the ventricle. The cause of the flutter was known in three patients (ischaemic heart disease, alcoholic cardiomyopathy, and dilated cardiomyopathy). In the remainder, though the aetiology of the arrhythmia was unknown, three had evidence of impaired left ventricular function caused by primary myocardial disease or perhaps a response to chronically rapid ven-

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Table 1 Patient details

Case No	*Age/sex*	*Type*	*Flutter cycle length (ms)*	*Duration (mnth)*	*Medications*	*Aetiology*	*LV EDD/ESD (cm)*	*LA size (cm)*
Group 1:								
1	50/M	Chronic (type I) 1:1	220	17	Di	DCM	6·5/5·9	4·8
2	64/M	Chronic (type I)	250	21	A, D, Di, F, P, S, V	Lone	6·0/4·5	4·0
3	67/M	Chronic (type I)	210	36	A, At, Di	IHD	6·1/4·8	4·4
4	39/M	Chronic (type I) 1:1	240	39	A, Di, F, P, S	Lone	5·5/4·2	4·8
Group 2:								
5	62/M	Chronic (type I)	280	11	A, At, Di	Alcoholic	5·2/4·2	3·8
6	58/M	Paroxysmal (type I)	225	7	D, F, P, S	Lone	5·3/3·4	4·2
7	58/M	Paroxysmal	250	8	A, At, D, F, V	Lone	6·1/4·8	4·6

A, amiodarone; AT, atenolol; D, disopyramide; Di, digoxin; F, flecainide; P, propafenone; V, verapamil; DCM, dilated cardiomyopathy; EDD, end diastolic dimension; EF, left ventricular ejection fraction; ESD, end systolic dimension; IHD, ischaemic heart disease.

tricular rates. Two patients had associated atrioventricular conduction disease. Alcohol ablation of the atrioventricular node by a transcoronary approach had previously been considered in two patients but had been abandoned because of difficulty in cannulating the atrioventricular nodal artery. One further patient had previously undergone unsuccessful high energy ablation of the atrioventricular node which had been complicated by a period of hypotension.

In the group 1 patients the primary aim of the procedure was to ablate the atrioventricular node and His bundle. Group 1 patients were drawn from a total of six patients with atrial flutter/fibrillation in whom we had used a modified low energy power source to attempt abolition of atrioventricular conduction. Group 2 patients were those in whom selective ablation of atrial tissue in the triangle of Koch was planned.

METHODS

All ablation procedures were performed under general anaesthesia. A 6F bipolar pacing electrode was introduced via the subclavian vein and then positioned in the right ventricular apex. The 7F bipolar electrode that was to be used for delivery of the ablative shock was then introduced via the right femoral vein and placed across the tricuspid valve to record the His bundle potential. All recordings were displayed on a Siemens Elema Mingograf 82 jet recorder at a paper speed of 100 mm/s. In those patients undergoing His bundle ablation (group 1) the ablating catheter was gradually withdrawn until a large low right atrial signal was obtained while a His potential deflection was just maintained. A low energy shock (<25 J) was then delivered with a specially modified energy source (Cardiac Recorders CR60) the characteristics of which have been previously described.[9,10] If atrioventricular conduction resumed after the initial shock then further shocks were given until stable complete heart block was achieved (table 2). Temporary ventricular pacing was started and continued until a permanent pacing system was implanted.

In group 2 patients a quadripolar electrode was introduced via the subclavian vein and placed in the coronary sinus. This allowed accurate visualisation of the course of the vessel. In these patients the ablation catheter was again positioned to record a His potential. This localised the position of the His bundle and defined the apex of the triangle of Koch (fig 1). Then we withdrew this catheter using clockwise torque to rotate the tip posteriorly towards the os of the coronary sinus. Catheter manipulation was performed under single plane fluoroscopy in the anteroposterior projection to verify each position in a right anterior projection, which gave optimal visualisation of the low posterior right atrium. An initial shock of 5 J was delivered near the apex of Koch's triangle at a site where the His bundle deflection was no longer visible (fig 2). If atrioventricular conduction was not compromised by this, a further shock of 10 J was delivered at the same site. Multiple further shocks were then delivered covering as much of the surface area of the triangle as was technically feasible. Particular care was taken to ensure that several shocks were delivered not only around the mouth of the coronary

Table 2 Ablation details

Case No	*Shocks (J)*	*Cumulative energy (J)*	*Effect on atrioventricular conduction*	*Outcome*	*Follow up (mnth)*
Group 1:					
1	30, 30, 40	100	3° block for < 1 mnth. 1° block long term	Sinus rhythm	14
2	20, 20, 20, 20, 20, 20, 20, 20, 20, 20	200	3° block for < 1 mnth. No effect long term	Sinus rhythm	7
3	5, 10, 20, 20, 20, 20, 25, 25, 50, 50	245	3° block for < 1 mnth. 1° block long term	Sinus rhythm	3
4	400, 400, 25, 25, 25	800 + 75	3° block for < 1 h. Nil long term	Sinus rhythm	7
Group 2:					
5	5, 5, 5, 5, 5, 10, 10, 10, 10, 10, 10, 15, 15	110	Nil	Sinus rhythm	3
6	5, 5, 5, 10, 10, 10, 10, 15, 15, 15, 15, 15	130	Nil	Developed atrial fibrillation at two mnth	2
7	5, 10, 10, 10, 15, 15, 15, 15, 20, 20, 20, 20, 20, 20, 20	235	1° block for < 10 beats	Recurrence of atrial flutter at one mnth	2

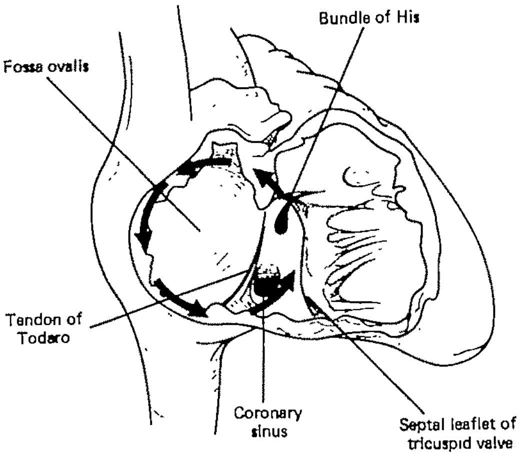

Figure 1 Anatomical boundaries of the triangle of Koch. Apex = His bundle; sides = tendon of Todaro, and septal leaflet of tricuspid valve. The base runs through the coronary sinus. Broad arrows indicate the putative re-entrant circuit in type 1 atrial flutter.

sinus but also just within the os. Energies of up to 20 J were used at sites not immediately adjacent to the area of the atrioventricular node. The procedure was stopped when at least two shocks had been delivered at each attainable site. We then attempted to induce atrial flutter using single extrastimuli and rapid atrial pacing. All patients were followed up at one month and three months after discharge from hospital.

Results

In group 1 all patients were in chronic atrial flutter at the time of the procedure. In three patients stable complete heart block was achieved after three to 10 shocks with a cumulative energy of 100–245 J. The single largest energy used was 50 J. All of these patients had permanent adaptive rate pacing systems implanted and at discharge did not need antiarrhythmic treatment. At subsequent follow up (range three to 14 months) these patients remained symptom free. All had evidence of a return of atrioventricular conduction with two showing first degree atrioventricular block. In patient 4 high energy ablation of the atrioventricular node was attempted with two 400 J shocks. Only transient atrioventricular block was achieved but the patient developed hypotension with a systolic blood pressure of 60 mm Hg. The procedure was therefore stopped. Two days later attempted low energy ablation produced only temporary atrioventricular block. This patient was discharged on antiarrhythmic treatment to await surgical ablation of the atrioventricular node. However, he suffered no recurrences of his symptoms and his antiarrhythmic treatment was gradually withdrawn.

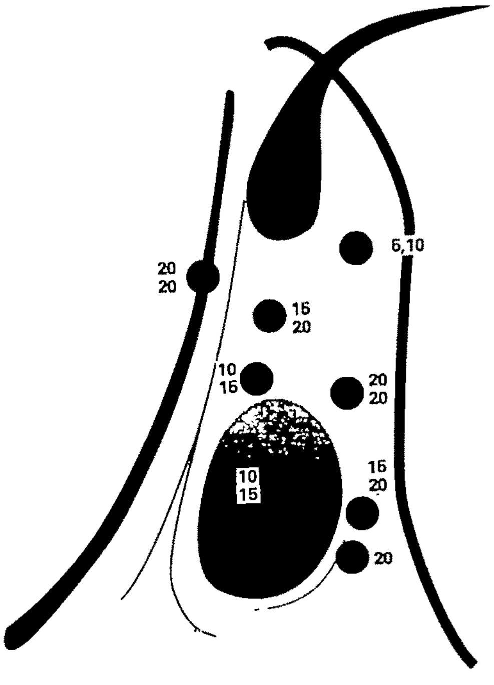

Figure 2 Triangle of Koch enlarged showing the approximate sites and magnitudes of energy delivered in joules.

In group 2 patients 12–15 shocks were delivered with a cumulative energy of 105–235 J. The single maximum energy used was 25 J. During the procedure one patient developed evidence of transient first degree atrioventricular block that lasted less than 10 beats. At the end of the procedure atrial flutter could still be induced in two patients. At follow up of three to four months two patients remained free of atrial flutter. Of these, one patient had developed atrial fibrillation, an arrhythmia that had not been documented before ablation. In the third patient atrial flutter recurred a month after the procedure.

COMPLICATIONS

No patient developed hypotension or evidence of ventricular arrhythmia during low energy ablation. In group 2 one patient with alcoholic cardiomyopathy developed mild congestive heart failure one week after the procedure. This responded satisfactorily to diuretic treatment.

Discussion

Our experience suggests that the substrate for atrial flutter can be ablated by multiple low energy shocks in the triangle of Koch without the need for extensive endocardial mapping. In 1925 Lewis first suggested that atrial flutter was due to a macro-reentry circuit in the right atrium. There is now considerable evidence to support this hypothesis from both experimental models of the arrhythmia and from clinically based electrophysiology studies.[7 11 12] The typical form of the arrhythmia (type 1) in humans is characterised by negative flutter waves in the inferior leads of the surface electrocardiogram. The arrhythmia can be entrained by rapid atrial pacing and reset by appropriately timed atrial extrastimuli, suggesting a reentry mechanism with an excitable gap. Endocardial mapping of the arrhythmia shows that activation proceeds in an anticlockwise direction from the os of the coronary sinus to the bundle of His, then to the high right atrium, and finally to the lateral wall of the atrium before returning to the os of the coronary sinus thereby completing the circuit[13 14] (fig 1).

Waldo first developed the concept of entrainment of reentrant arrhythmias based on his observations of atrial pacing in patients with postoperative atrial flutter.[15] Central to this concept of entrainment is the presence of both an excitable gap and an area of slow conduction within the reentrant circuit. The ability to entrain an arrhythmia is now widely accepted as proof that the arrhythmia is caused by a reentrant mechanism. However, direct proof that the circuit of atrial flutter contains an area of slow conduction has only recently been obtained.[3 16 17] The most convincing evidence comes from Klein and colleagues who reported two patients with atrial flutter in whom intraoperative epicardial mapping confirmed the atrial activation sequence demonstrated by the intracardiac catheter approach. In addition there was a clumping of isochrones in the postero-inferior right atrium between the os of the coronary sinus and the atrioventricular node indicating slowed conduction in this region. After cryoablation of this area neither patient experienced a recurrence of their arrhythmia. Whether the posteroinferior right atrium is an obligatory part of the flutter circuit and consistently shows slow conduction has not been definitively established. It has been suggested that this area of slow conduction can be identified by mapping of the atrium during entrainment of atrial flutter and by assessment of the tachycardia response to attempted reset by atrial extrastimuli. This procedure termed entrainment mapping is one of the methods used to localise the area of slow conduction before ablation.[17 18]

Recently several workers have suggested that fractionated or double spike electrograms may be a marker for the area of slow conduction.[19–21] These can be recorded during spontaneous or entrained flutter in most patients and also occasionally during atrial pacing or sinus rhythm. They are found most consistently in the triangle of Koch but have also been recorded at other right atrial sites remote from this region. Although some workers suggest that these electrograms, particularly those with a double spike configuration, bracket the area of slow conduction on the circuit others argue that they represent colliding wavefronts within the refractory core around which the arrhythmia circulates. Whether these abnormal electrograms are simply epiphenomena or truly represent the area of slow conduction remains controversial. Both groups that have previously reported high energy DC ablation of atrial flutter regard the recording of these abnormal electrograms as the most important way of identifying the most suitable area for ablation. In some patients they recorded fractionated electrograms in more than one area of the right atrium. In practice they ablated only in the triangle of Koch. We achieved remission and possibly long term cure of the arrhythmia by delivering shocks in this region without resorting to complex endocardial mapping.

The fact that attempted His bundle ablation also prevented recurrences of atrial flutter in some patients suggests that shocks delivered at the apex of the triangle of Koch may alter the conduction characteristics within a wider area of the triangle thereby abolishing or favourably modifying the arrhythmia substrate. However, ablation in this area may have additional unwanted electrophysiological consequences. One patient in our group and three patients in the series of Saoudi *et al* developed previously undocumented atrial fibrillation after ablation. The procedure may have disrupted but not abolished the arrhythmia substrate giving rise to recurrent episodes of unstable atrial flutter that degenerated into atrial fibrillation. Alternatively, modification of the surrounding atrial myocardium may have predisposed it to primary atrial fibrillation. Ablation in the right atrium therefore seems to alter the electrophysiological substrate in some patients in such a way that the flutter circuit can either no longer be engaged or followed but fibrillation, which does not require this discrete zone of slow conduction, may be facilitated.

Not all patients undergoing His bundle ablation either in our own or other series have shown abolition of atrial flutter. In some patients, but not all, this secondary effect on the flutter circuit may have been masked by successful interruption of atrioventricular conduction. This variable success in ablating the flutter circuit is probably attributable to differing extents of tissue damage. In some patients though atrial muscle at the apex of Koch's triangle had been ablated other areas within the triangle could provide alternative conduction paths for the circulating wavefront. Only by abolishing all potential paths through this isthmus would the area of slow conduction be adequately extirpated. Use of a single high energy DC shock in this area ablates not only a few millimetres around the catheter tip but also modifies the conduction characteristics of the surrounding tissue for several square centimetres.[22] If low energy shocks were to be used then several lesions would be required throughout the triangle to ensure that all potential paths for the arrhythmia had been ablated.

The use of intracardiac high energy DC shock has been associated with early cardiac perforation and long term impairment of exercise capacity by right ventricular damage. This damage is probably mediated by arcing and barotrauma. Experimental work suggests that these are related to the maximum energy used, whereas useful tissue damage is related to peak voltage. The energy source that we used was designed to deliver capacitive discharges with a short time constant by an anodal discharge. The shorter time constant means that though the peak voltage and current achieved were unchanged the total charge and energy were reduced. When used with a specially designed ablation catheter with a contoured tip peak voltages of up to 1423 V can be achieved before arcing occurs.[23] This minimises gas formation, arcing, and barotrauma to the surrounding cardiac structures.[24] Most shocks delivered in our patient group, though well below the high energies of 150–300 J used by other groups, were above the arcing threshold for the system when used with a standard 7F ablation catheter. Therefore some degree of arcing and barotrauma must have occurred which, it could be argued, may have contributed not only to the overall effectiveness of the procedure but might also result in long term impairment of cardiac function. In addition, though it is possible, there is no conclusive proof that the barotrauma caused by multiple low energy shocks is less than that caused by a single high energy shock if the same cumulative energies are used. In future, improved power sources and catheter design may make ablation of the flutter substrate possible without causing any barotrauma. In the meantime, if our simplified approach to the procedure shows continued success in the long term, it will increase the applicability of the technique to a wider group of patients.

CONCLUSION

Catheter ablation in the low posterior right atrium can be successfully used to ablate the substrate of atrial flutter. The use of low energy shocks may help to minimise the effects of barotrauma. The performance of the procedure can be guided by the simple anatomical landmarks of the triangle of Koch rather than by using extensive endocardial mapping techniques.

1 Evans GT, Scheinman MM, and the Executive Committee of the Registry. The percutaneous cardiac mapping and ablation registry: final summary of results. *PACE* 1988;11:1621–6.

2 Schofield PM, Bowes RJ, Brooks N, Bennett DH. Exercise capacity and spontaneous heart rhythm after transvenous fulguration of atrioventricular conduction. *Br Heart J* 1986;56:358–65.

3 Klein GJ, Guiraudon GM, Sharma AJ, Milstein S. Demonstration of macroreentry and feasibility of operative therapy in the common type of atrial flutter. *Am J Cardiol* 1986;57:587–91.

4 Saoudi N, Atallah G, Kirkorian G, Touboul P. Catheter ablation of the atrial myocardium in human type 1 atrial flutter. *Circulation* 1990;81:762–71.

5 Chauvin M, Brechenmacher C. A clinical study of the application of endocardial fulguration in the treatment of recurrent atrial flutter. *PACE* 1989;12:219–24.

6 Touboul P, Saoudi N, Atallah G, Kirkorian G. Electrophysiologic basis of catheter ablation in atrial flutter. *Am J Cardiol* 1989;64:79J–82J.

7 Boineau JP, Schuessler RB, Mooney CR, Miller CB, Wylds AC, Hudson RD, *et al*. Natural and evoked atrial flutter due to circus movement in dogs. *Am J Cardiol* 1980;45:1167–81.

8 Boyden PA. Activation sequence during atrial flutter in dogs with surgically induced right atrial enlargement. *Circ Res* 1988;62:596–608.

9 Cunningham D, Rowland E, Rickards AF. A new low energy power source for catheter ablation. *PACE* 1986;9:1384–90.

10 Rowland E, Cunningham D, Ahsan A, Rickards A. Transvenous ablation of atrioventricular conduction with a low energy power source. *Br Heart J* 1989;62:361–6.

11 Inoue H, Matsuo H, Takayanagi K, Murao S. Clinical and experimental studies of the effects of atrial extrastimulation and rapid pacing on atrial flutter cycle. Evidence of macroreentry with an excitable gap. *Am J Cardiol* 1981;48:624–31.

12 Disertori M, Inama G, Vergara G, Guarnerio M, Del Farvero A, Furlanello F. Evidence of a reentry circuit in the common type of atrial flutter in man. *Circulation* 1983;67:434–40.

13 Puech P, Latour H, Grolleau R. Le flutter et ses limites. *Arch Mal Coeur* 1970;63:116–44.

14 Chang B-C, Schuessler RB, Stone CM, Branham BH, Canavan TE, Boineau JP, *et al*. Computerised activation sequence mapping of the human atrial septum. *Ann Thorac Surg* 1990;49:231–41.

15 Waldo AL, MacLean WAH, Karp RB, Kouchoukos NT, James RM. Entrainment and interruption of atrial flutter with atrial pacing: studies in man following open heart surgery. *Circulation* 1977;56:737–45.

16 Olshansky B, Okumura K, Henthorn RW, Epstein AE, Plumb VJ, Waldo AL. Entrainment of human atrial flutter localises the area of slow conduction in the inferior right atrium [abstract]. *J Am Coll Cardiol* 1986;7:128A.

17 Josephson ME, Buxton AE, Almendral JM, Gottlieb CD. Electrophysiologic characteristics of atrial flutter and their therapeutic implications. In: Attuel P, Coumel P, Janse MJ, eds. *The atrium in health and disease*. Mount Kisco, New York: Futura Publishing Company, 1989:95–132.

18 Waldo AL, Henthorn RW. Use of transient entrainment during ventricular tachycardia to localise a critical area in the reentry circuit for ablation. *PACE* 1989;12:231–44.

19 Cosio FG, Arribas F, Palacios J, Tascon J, Lopez-Gil M. Fragmented electrograms and continuous electrical activity in atrial flutter. *Am J Cardiol* 1986;57:1309–14.

20 Cosio FG, Arribas F, Barbero JM, Wallmeyer C, Goicolea A. Validation of double spike electrograms as markers of conduction delay or block in atrial flutter. *Am J Cardiol* 1988;61:775–80.

21 Olshansky B, Okumura K, Henthorn RW, Waldo AL. Characterisation of double potentials in human atrial flutter: Studies during transient entrainment. *J Am Coll Cardiol* 1990;15:833–41.

22 Moak JP, Friedman RA, Garson A. Electrical ablation of atrial muscle. 1. Early and late anatomic observations in canine atria. *Am Heart J* 1987;113:1397–404.

23 Ashan AJ, Cunningham D, Rowland E, Rickards AF. Catheter ablation without fulguration: design and performance of a new system. *PACE* 1989;12:131–5.

24 Bardy GH, Coltorti F, Ivey TD, Alferness C, Rackson M, Hansen K, *et al*. Some factors affecting bubble formation with catheter-mediated defibrillator pulses. *Circulation* 1986;73:525–38.

Br Heart J 1992;67:72–9

Early and late arrhythmias after the Fontan operation: predisposing factors and clinical consequences

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Abstract

Objective—**To study the incidence, predisposing factors, and clinical significance of arrhythmias early and late after the Fontan operation for congenital heart disease.**

Patients and methods—**All 104 consecutive patients undergoing Fontan repair from 1975 to 1988 were studied retrospectively. Hospital records were reviewed for perioperative arrhythmia. Clinical information and annual electrocardiograms were available for all 78 hospital survivors during a follow up of up to 13 years (mean 3·7 years). Ambulatory electrocardiographic monitoring was performed in 67 patients (81%).**

Results—**Eleven patients (10·6%) developed a perioperative tachycardia (eight, atrial flutter; three, His bundle tachycardia). Multivariate analysis showed that raised preoperative mean pulmonary artery pressure and low aortic saturation were significant risk factors for the development of atrial flutter ($r^2 = 0{\cdot}32$, $p = 0{\cdot}0001$) but not for His bundle tachycardia. Despite intensive medical treatment 10 of these 11 patients died. At the last visit 72 (92%) of the 78 patients were in sinus rhythm on their standard 12 lead electrocardiogram. Junctional rhythm was present in three patients, two patients had atrial flutter, and one had a paced rhythm. Ambulatory monitoring did not show important bradycardia or ventricular arrhythmias. Actuarial survival free of supraventricular arrhythmia was 82% at eight years after operation. Multivariate analysis identified older age, increased right atrial size, and raised mean preoperative pulmonary artery pressure as risk factors for arrhythmia during intermediate follow-up ($r^2 = 0{\cdot}46$, $p < 0{\cdot}001$). Late tachycardias, in contrast to those occurring in the perioperative period, were not associated with an increased mortality.**

Conclusions—**Except for His bundle tachycardia in the perioperative period, early and late arrhythmias after a Fontan operation seem to be a consequence of adverse preoperative and postoperative haemodynamic function. The perioperative outcome is therefore poor even when the patient can be restored to sinus rhythm. Medical and surgical modifications to improve the haemodynamic disturbances associated with arrhythmias are therefore indicated.**

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In 1971 Fontan described an operation to connect the right atrium to the pulmonary artery in patients with tricuspid atresia, without incorporating an adequate right ventricle in the circulation.[1] Modifications of this procedure are being used as the definitive surgical repair in patients with an increasingly wide range of complex congenital heart disease. All the various surgical techniques that have been advocated involve atrial surgery and result in a chronic increase in the systemic venous atrial pressure.[2 3] Both factors predispose to supraventricular arrhythmia.[4-7] The acute and chronic haemodynamic consequences of such arrhythmia, producing a rise in the pulmonary venous atrial pressure in a circulation that usually lacks a subpulmonary ventricle, may be serious. Little information on arrhythmia after the Fontan operation and its consequences has been published.[8] We therefore investigated a consecutive series of patients undergoing Fontan repair, to study the incidence, time course, and predisposing factors to early and late arrhythmia, and to identify the circumstances in which this may contribute to increased morbidity and mortality.

Patients and methods

PATIENTS

All 104 patients (62 male, 42 female) undergoing a Fontan operation between April 1975 and March 1988, and who were resident in the United Kingdom, were included in the study. Initially we used the strict selection criteria of Choussat *et al*[9] but over the course of the study several modifications and exceptions were introduced. As a result, a wide variety of anomalies and surgical connections are represented in the patient population (table 1). Early on, valved conduits from the right atrium to right venticle or right atrium to pulmonary artery were inserted but later only direct atriopulmonary or total cavopulmonary connections were performed. Biographical information, morphological diagnosis, details of previous surgery, haemodynamic variables before Fontan operation, surgical technique, and follow-up status were available in all patients.

Table 1 Morphological and surgical characteristics

Diagnosis	*Tricuspid atresia*		*Pulmonary atresia (IVS)*		*Complex*		*Total*	
Hospital survivor	+	−	+	−	+	−	+	−
Total:	42	12	12	7	24	7	78	26
Blalock-Taussig	28 (8)	8	12 (4)	3	16 (3)	3 (1)	56 (15)	14 (1)
Waterston	5	2		2	1		6	4
Potts	1						1	
Central shunt		1	1	1			1	2
Pulmonary band	3	2			5 (2)	2	8 (2)	4
Coarctectomy + band	2	1					2	1
Brock			1	4			1	4
Glenn	2						2	
Blalock-Hanlon					1	1	1	1
No surgery	6				4	1	10	1
Fontan connection:								
RA-RV	9 (5)	2		1			9	3
RA-PA conduit	10 (1)	1	3	3	5	1	18	5
RA-PA direct	21	9	6	2	7	5	34	16
TCPC	2		2	1	12	1	17	2

IVS, intact ventricular septum; RA, right atrium; RV, right ventricle; TCPC, total cavopulmonary connection. Second similar operations are indicated in parentheses.

METHODS

Hospital records, including drug charts and notes from the intensive care unit, were reviewed for arrhythmia which occurred before and during admission to hospital for operation and required intervention such as pacing, cardioversion, or antiarrhythmic treatment. Twelve hours after operation and just before the onset of an arrhythmia we assessed the patient's haemodynamic condition by examining right atrial pressure, transpulmonary gradient, diuresis, blood pressure, inotropic support, and the requirement for dialysis or abdominal counterpulsation.

Follow up information was obtained in all patients, either by outpatient assessment or by contact with the patient's family and primary physician. Patients and parents were questioned about the functional status and symptoms of arrhythmias. Follow up records and serial electrocardiograms obtained at least annually were also reviewed for symptoms and objective evidence of rhythm disturbance.

AMBULATORY MONITORING

In 67 patients 24 hour ambulatory electrocardiographic monitoring was performed 0·2–13 (mean 3·4) years after the Fontan procedure. Care was taken to monitor all patients in whom clinical follow up suggested an arrhythmia. Oxford Medilog 2 channel recorders were used (CM1 and CM5 leads) and tapes were analysed visually at 60 times real time with an Oxford Medilog playback unit. The basic cardiac rhythm and the presence of arrhythmias or conduction defects were noted. Patients were considered to be in stable sinus rhythm if this was present for $>90\%$ of the 24 hour period. Records were classified as intermittent sinus and junctional rhythm if junctional escape rhythm was present in 10–50% of the recording and junctional rhythm if this was present $>50\%$ of the time. Atrial and ventricular extrasystoles were counted and ranked as proposed by Nagashima *et al*[10]: <4, 5–9, 40–49, or >50 extrasystoles per 24 hour period. The presence of complex forms including multiform beats, couplets, and runs of ventricular tachycardia ($\geqslant 3$ consecutive ventricular extrasystoles at a heart rate of >120 beats/min) was also noted.

EXERCISE TESTING

Supine graduated exercise testing on a bicycle ergometer was performed by 73% (46 patients) of the survivors over the age of 5·5 years in whom stress testing was considered feasible. Patients were exercised for five minutes at progressively increasing workloads from 0·25 W/kg to 1·5 W/kg with 0·25 W/kg increments per minute. Heart rate and rhythm were monitored continuously. Rate was expressed as a function of an age-predicted value derived from data in 28 age-matched controls studied in our laboratory.

HAEMODYNAMIC STATUS

Routine postoperative cardiac catheterisation was not performed but catheterisation data were available in 28 (32%) of survivors. In 47 patients (60%) echocardiography was used to study ventricular size and contractility and atrial size. Except for the patients with a total cavopulmonary connection, the length and width of the atria were measured from the apical view and their product divided by the body surface area to obtain an index of atrial size. In the patients who developed chronic atrial arrhythmias data were obtained from echocardiograms recorded when the patient was last seen in sinus rhythm.

STATISTICAL ANALYSIS

Data were stored in a SIR (version 2) database on an Amdahl mainframe computer and analysed with SAS statistical packages (SAS Institute, Cary, North Carolina, USA). All data were expressed as mean with standard deviation and/or range. Actuarial analysis of late survival free of supraventricular arrhythmias (as detected by any method and using the time of operation as time zero), was made by the Kaplan–Meier method. Univariate analysis and multiple regression techniques were used to determine risk factors for perioperative and late postoperative arrhythmias. Chi squared statistics were used to study differences of proportions; independent testing and repeated-measures analysis of variance were used to compare the exercise results of the Fontan patients with those of age-matched controls.

Results

PATIENT CHARACTERISTICS

Table 1 summarises the morphological and surgical characteristics of the patients. Almost all (93 patients (89%)) had undergone palliation before the Fontan procedure, either by banding of the pulmonary trunk, by shunt procedures, or by other miscellaneous interventions. Their mean (SD) age at Fontan operation ranged from 0·9 to 18·3 years (7·12 (3·9)) and the 78 (75%) hospital survivors were followed for 0·2–13 years (3·7 (3·3)). At the last assessment, 27 patients (36%) were taking cardiac medication (digitalis in 18, diuretics in seven, vasodilators in nine, other antiarrhythmic agents in nine, anticoagulants in five). Sixty four patients were in New York Heart Association class I, 10 in class II, and one in class III. Three patients had died during follow up—two at re-operation and one two months after Fontan operation.

PERIOPERATIVE ARRHYTHMIA: BRADYCARDIA

During the first 24 hours after operation (mean onset 6·3 hours) eight (7·7%) patients had a bradycardia requiring specific treatment. In three it was sinus bradycardia (rates 50, 62, 68 beats/min) and in five patients a slow junctional escape rhythm (range 50–72 beats/min, mean 58). Atrial pacing (five patients) and/or isoprenaline (seven patients) was effective and improved the haemodynamic condition of all the patients. In six treatment was stopped after 8–72 hours (mean 31) but two patients with persistent sinus bradycardia were discharged on oral isoprenaline for two and three months respectively (60 and 67 beats/min under treatment). Two of the patients with early significant bradycardias subsequently developed atrial flutter 25 and 72 hours later with accompanying rapid deterioration of their haemodynamic condition. One died and the other was restored to sinus rhythm after amiodarone and electrical cardioversion. He has remained in intermittent sinus and junctional rhythm over a four year follow up period on amiodarone. Atrial flutter recurred after some months on the one occasion when medication was stopped. Of the remaining six patients, one has developed atrial flutter 14 months after Fontan. On ambulatory monitoring (1–7, mean 3·5 years after surgery) three of these patients were in sinus rhythm with frequent (>200 in 24 hours) atrial extrasystoles. This feature was seen in only two of 55 patients with no perioperative bradycardia in whom ambulatory electrocardiographic monitoring was performed. Thus perioperative bradycardia though not associated with increased mortality was associated with an increased incidence of late arrhythmias ($p < 0{\cdot}001$).

ATRIOVENTRICULAR BLOCK

Persistent complete atrioventricular block after the Fontan operation in two patients with a double inlet ventricle. Both were treated in the perioperative period with atrioventricular sequential pacing and a DDD pacemaker was implanted in one patient after one month because of a slow junctional rhythm (30 beats/min). The other patient had considerable left ventricular dysfunction and poor haemodynamic function with a spontaneous ventricular rate of 60 beats/min. The clinical condition did not improve with atrioventricular sequential pacing and he died two months after operation while awaiting cardiac transplantation. No other patient developed atrioventricular block.

TACHYCARDIA

Tachycardias developed in 11 patients during the early postoperative period. One girl developed atrial fibrillation as she was weaned from bypass (right atrial pressure 17 mm Hg). Despite an acceptable ventricular rate on multiple antiarrhythmic agents and several attempts at cardioversion she remained in a low output state. While she was being prepared for a take-down of her Fontan operation four hours after the initial operation she died in ventricular fibrillation. A further five patients developed atrial flutter in the first 24 hours after operation (1–24, mean 9 hours). In all the arrhythmia was preceded by poor haemodynamic function reflected by high right atrial pressure (19–23, mean 21 mm Hg), low urinary output and the need for maximal inotropic support, and abdominal counterpulsation (two patients). All died 1–8 days after the Fontan operation despite early conversion to sinus rhythm in three patients (overdrive pacing 1, electrical cardioversion 2) and improvement in ventricular rate in two with amiodarone. A further patient collapsed suddenly while in sinus rhythm after successful weaning from the ventilator half an hour after extubation on the third postoperative day. After resuscitation he was found to be in atrial flutter and was successfully converted by overdrive pacing to sinus rhythm. Despite the absence of any further arrhythmia he died 20 days later of a pulmonary infection. Only one patient, who developed atrial flutter three days after surgery, survived. He was successfully returned to sinus rhythm by electrical cardioversion after treatment with intravenous amiodarone.

A further three patients developed a His bundle tachycardia (rate 162–200, mean 175 beats/min) within three hours of operation. Before the tachycardia all three patients had satisfactory haemodynamic function as reflected by a low (<15 mm Hg) systemic venous pressure, good cardiac output, and diuresis with minimal support. The tachycardia rate was not successfully controlled (by digoxin and atrioventricular sequential pacing) in one patient and despite good early haemodynamic function he died three hours after onset of the arrhythmia. In the second and third patients amiodarone and overdrive atrioventricular sequential pacing slowed the automatic tachycardia and improved the haemodynamic condition, but despite this both patients died one and seven days later at attempted take-down of the Fontan operation.

Multivariate analysis produced a significant model ($r^2 = 0{\cdot}32$, $p < 0{\cdot}0001$) predicting the occurrence of perioperative atrial flutter with a mean preoperative pulmonary artery pressure of >16 mm Hg ($p = 0{\cdot}002$), low preoperative aortic saturation ($p = 0{\cdot}041$), and young age at Fontan operation ($p = 0{\cdot}086$). There were too few patients with His bundle tachycardia to perform a risk factor analysis. However, there were no specific features that identified these patients even on retrospective analysis, and these patients clearly did not fit the profile of those patients who developed perioperative atrial flutter.

RESULTS DURING INTERMEDIATE FOLLOW UP

Three of 78 hospital survivors died during follow up. None of the deaths, however, seemed to be related to an arrhythmia. One patient with double inlet left ventricle had borderline preoperative haemodynamic function (mean pulmonary artery pressure 27 mm Hg, left ventricular dysfunction with atrioventricular valve regurgitation) and the result of his Fontan operation was poor (mean right atrial pressure 20 mm Hg one week after operation). He had developed complete atrioventricular block postoperatively (see above) but the haemodynamic condition had not improved with atrioventricular sequential pacing. He died two months after the Fontan operation. Two other patients died 5·1 and 7·5 years after the Fontan repair, both at the time of the second replacement of a right atrial to pulmonary artery valved conduit. Both patients had 24 hour ambulatory monitoring performed after the first operation and before the second operation. One was in sinus rhythm throughout and the other had short periods of supraventricular tachycardia alternating with sinus bradycardia and pauses of up to two seconds. He had a pacemaker inserted because of dizzy spells. However, this failed to improve his symptoms, which were then attributed to low cardiac output secondary to severe obstruction of his conduit. No other cases of late bradycardia were detected.

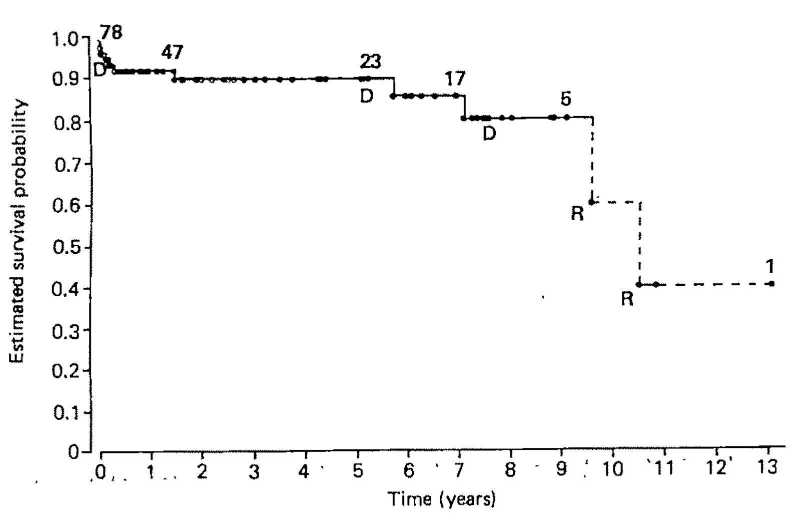

Figure 1 Actuarial survival free of supraventricular tachycardia after the Fontan operation (Kaplan–Meier method with time of operation as time zero). Each patient withdrawn is represented by a circle; the three late deaths (D) are indicated. R = redo Fontan with atrial flutter in early convalescence (n = 2).

Eleven patients (14% of postoperative survivors) experienced a paroxysmal tachycardia during their late postoperative course as detected by clinical examination, routine electrocardiography, ambulatory monitoring, or exercise testing. One of these was the only survivor of a tachycardia in the perioperative period (see above). Atrial flutter recurred a few months after an attempt at stopping amiodarone treatment. It was restarted and he has been successfully maintained in intermittent sinus and junctional rhythm. A further five patients developed clinical or electrocardiographic evidence of tachycardia shortly after discharge from hospital, all while doses of digitalis and diuretics were being tapered off (mean interval after operation 1·9 months, range 2 weeks to 4 months). In three there was only clinical evidence of short bouts of tachycardia and symptomatic palpitation with no haemodynamic upset. Repeated ambulatory electrocardiographic monitoring did not detect objective evidence of an arrhythmia in these patients. The two other patients were admitted to hospital in atrial flutter with 2:1 atrioventricular block and a ventricular rate of 180 beats/min. Both were cardioverted to sinus rhythm. There has been no subsequent arrhythmia on chronic medication with digitalis in one or flecainide in the other. In three patients late tachycardias were related to problems with conduit obstruction. One patient with severe obstruction of his second valved conduit between the right atrium and right ventricle had short runs of supraventricular tachycardia (rate 120 beats/min) during ambulatory electrocardiographic monitoring. He died at second reoperation. Two other patients developed atrial flutter with only mild haemodynamic upset one and three months after reoperation for conduit obstruction. Sinus rhythm was re-established and maintained with amiodarone in one patient and the ventricular rate was controlled with flecainide in the other. Two patients developed new atrial flutter more than a year after the Fontan operation. One of these patients had been treated for sinus bradycardia in the perioperative period and had been discharged on oral isoprenaline for three months. Postoperative treatment with diuretics was stopped only at a 14 months evaluation and when she was reviewed at 22 months she was noted to be in atrial flutter with a ventricular rate of 140 beats/min. This change in rhythm was associated with a significant increase in ventricular size and impaired left ventricular contractility. The other patient was admitted to an emergency department seven years after his Fontan operation: he had atrial flutter and a ventricular rate of 220 beats/min associated with impaired haemodynamic function. He had noticed occasional episodes of palpitation over the previous month with one syncopal episode. He was treated with intravenous verapamil, which initially produced some slowing of the heart rate which then, however, deteriorated to asystole. He was resuscitated but experienced a severe multiorgan ischaemic insult and has made only a slow recovery.

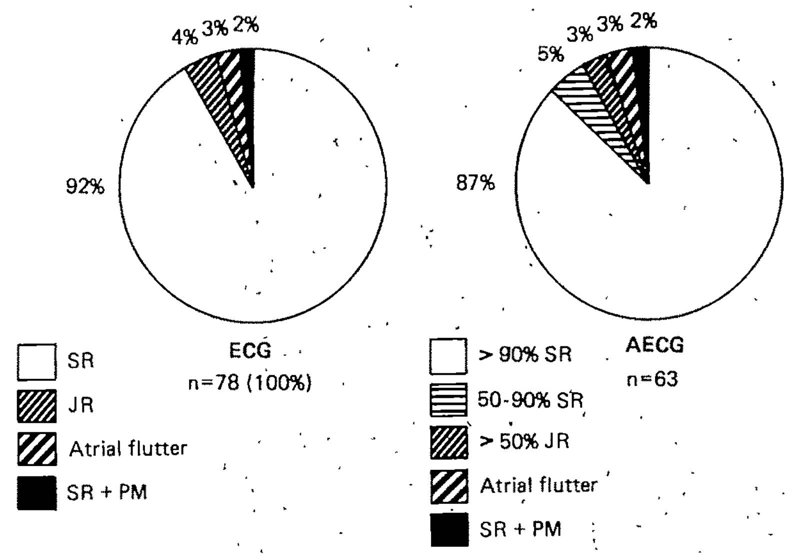

Figure 2 Cardiac rhythm in Fontan patients on last electrocardiogram (ECG) and on 24 hour ambulatory electrocardiographic monitoring (AECG). JR, junctional rhythm; SR, sinus rhythm; PM, pacemaker.

Actuarial analysis showed that survival free of tachycardias detected by any method was 89% at five years and survival at eight years after a successful Fontan operation was 82% (fig 1). Nine of the 11 patients with late tachycardia reported symptoms (five mild, three moderate, one severe).

ROUTINE ELECTROCARDIOGRAMS

At last visit, 72 of the 78 (92%) patients were in sinus rhythm on their standard 12 lead electrocardiograms (fig 2). Junctional or low right atrial rhythm was present in three patients, two of whom had left isomerism. Two patients had atrial flutter and one had a paced rhythm. First degree atrioventricular block was present in three patients, all of whom were taking digitalis.

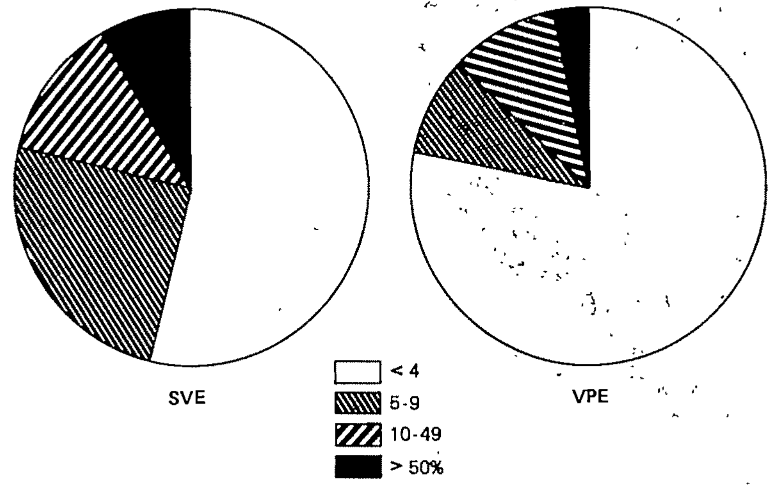

Figure 3 Supraventricular and ventricular extrasystoles (SVE and VE) on a 24 hour ambulatory electrocardiographic monitoring. Numbers refer to number of patients in each subgroup.

24 HOUR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Ambulatory monitoring was performed in 67 hospital survivors 3·5 (3·3) years after Fontan operation and 63 (81% of the total group) recordings were of adequate quality. Fifty five (87%) of these patients were in sinus rhythm. The remainder were in sinus rhythm with intermittent junctional escape (three patients), established junctional rhythm (2 patients), chronic atrial flutter (two patients), and one paced rhythm. Eight patients had a wandering atrial pacemaker during recordings. Figure 3 summarises the atrial and ventricular extrasystoles detected by ambulatory monitoring. Only two patients had more than 50 ventricular extrasystoles. All were isolated and uniform. One patient showed an episode of ventricular bigeminy at rest and one patient had two ventricular couplets. Five patients (8%) had more than 50 supraventricular extrasystoles in the 24 hour recording. No significant bradycardias or atrioventricular block were seen. Ambulatory monitoring detected evidence of arrhythmia with bouts of supraventricular tachycardia in only one patient and multiple recordings failed to detect arrhythmias in three patients with symptoms of palpitation and clinically documented tachycardias.

EXERCISE TESTING

All patients except one were in sinus rhythm throughout the exercise test. One patient with chronic atrial flutter had frequent uniform ventricular extrasystoles at rest which disappeared as soon as she started to exercise. Similarly, two other patients had frequent atrial extrasystoles at rest but these disappeared on exercise. No new ventricular arrhythmia was documented. At the highest workload of 1·5 W/kg the controls had a heart rate of 124 (18) beats per minute. The heart rate at rest was significantly higher in the Fontan patients than in the age-matched controls ($p < 0{\cdot}01$). This difference disappeared as soon as exercise started so that at all levels of exercise the heart rate in the Fontan patients was similar to that seen in age-matched controls.

FACTORS ASSOCIATED WITH LATE ARRHYTHMIA

Table 2 summarises factors that were assessed to determine risk factors for late arrhythmia. Multivariate analysis produced a significant model ($r^2 = 0{\cdot}46$, $p < 0{\cdot}001$) predicting occurrence of a tachycardia during intermediate follow up with older age ($p < 0{\cdot}01$), larger index of atrial size ($p < 0{\cdot}05$), and a preoperative mean pulmonary artery pressure > 20 mm Hg ($p < 0{\cdot}01$). Occurrence of frequent (> 50 per minute) atrial extrasystoles was predicted by a model ($r^2 = 0{\cdot}33$, $p < 0{\cdot}005$) which used time since Fontan repair ($p < 0{\cdot}003$) and preoperative mean pulmonary artery pressure as variables ($p < 0{\cdot}02$). In this study, we were unable to show a relation between the occurrence of arrhythmias during intermediate follow up and either the underlying cardiac lesion or the surgical technique.

Table 2 Factors included in the multivariate analysis for late tachycardia

	Late tachycardia		
No	*Absent*	*Present*	*t test (p)*
Age at Fontan operation (y)	7·3 (3·8)	10·1 (4·1)	<0·05
Follow up* (y)	3·5 (3·1)	4·3 (4·2)	NS
Age* (y)	10·9 (5·3)	14·4 (5·5)	<0·05
Preoperative haemodynamics (n = 78):			
Mean PA pressure (mm Hg)	14·0 (4·3)	13·9 (5·6)	NS
PA pressure >20 mm Hg	5/67	3/11	<0·01
Qp/Qs	1·6 (1·1)	1·7 (0·6)	NS
LVEDP (mm Hg)	9·3 (3·3)	8·1 (4·9)	NS
Aortic saturation (%)	83·8 (5·2)	86·2 (4·1)	NS
Echo data:			
LVEDD (%)	115 (15)	122 (13)	NS (n = 44)
Fractional shortening (%)	33·3 (5·9)	30·0 (6·6)	NS (n = 44)
RA width × length/BSA	26·8 (9·9)	36·6 (9·0)	<0·05 (n = 47)
LA width × length/BSA	9·6 (2·9)	11·2 (4·6)	NS (n = 47)
Cardiothoracic index	0·52 (0·05)	0·55 (0·13)	NS (n = 78)
Tallest P on ECG (mm)	3·0 (1·1)	2·5 (1·6)	NS (n = 78)

BSA, body surface area; LA, left atrium; LVEDD, left ventricular end diastolic dimension as % of normal for BSA[27]; LVEDP, left ventricular end diastolic pressure; PA, pulmonar artery; RA, right atrium. *Time to or age at end of follow up or occurrence of tachycardia.

Discussion

The Fontan operation and its modifications involve atrial surgery and may result in a circulation that functions at a chronically raised right atrial pressure. Both these factors are known to increase the likelihood of supraventricular arrhythmias. Our results show that the circulation after the Fontan operation is vulnerable to such tachycardias, particularly in the early postoperative period when they are highly associated with poor outcome. Late tachycardias, however, were better tolerated and did not provoke sudden death. These results contrast with published data from the Mayo Clinic in which 6/23 (26%) of the late deaths after Fontan surgery were sudden or attributed to arrhythmias.[11]

PERIOPERATIVE ARRHYTHMIA

The incidence of perioperative arrhythmias is undoubtedly underestimated because of the retrospective design of our study. Loss of sinus rhythm or ectopic rhythms that were transient and well tolerated will have been missed. Nevertheless, life threatening rhythm disturbances were noted in 10% of the patients. Without preoperative monitoring it is not possible to determine whether arrhythmias were already significantly more common in this group before the Fontan surgery. Certainly, some patients undergoing surgery have atrial isomerism, which is known to be associated with structural and electrophysiological abnormalities and loss of sinus rhythm.[12]

Two different patterns of perioperative tachycardias were noted. The most common was atrial flutter which was associated with borderline preoperative and postoperative haemodynamic function. Atrial flutter therefore seemed to be a marker that identified patients with adverse risk factors; moreover, when it did occur, atrial flutter triggered a rapid deterioration and accelerated an already existing decline in haemodynamic function. Acute and chronic changes in the electrophysiological properties of the atria in response to stretching and increase in pressure are well recognised. In the dog model, Boyden and Hoffman showed both increased susceptibility to initiation of atrial flutter and increased duration of arrhythmia in distended atria.[6] Potential substrates for arrhythmia have also been noted in studies on diseased human atria.[13] Furthermore, extensive atrial surgery as in the Mustard and Senning operation increases early arrhythmia. Puga *et al* and Matsuda *et al* reported a high incidence of severe atrial flutter after a modified Fontan technique in which a cavocaval channel was created with atrial wall for patients with left atrioventricular valve atresia or a single atrioventricular valve.[14 15] Sinus rhythm optimises systemic ventricular function. Though atrioventricular synchrony may not be required for survival,[16] the loss of the atrial contribution to systemic ventricular filling and increase in atrial pressure secondary to arrhythmias may seriously impair cardiac output after the Fontan operation.[17]

The poor outcome of the patients with postoperative atrial flutter emphasises the impact of patient selection on the results after Fontan operation. Both a raised preoperative mean pulmonary artery pressure and low aortic saturation were identified as significant risk factors for early atrial flutter. A raised pulmonary artery pressure is associated with some medial hypertrophy, which predisposes to increased pulmonary vascular resistance or reactivity or both.[18] The effects of hypoperfusion on the developing pulmonary circulation may be as deleterious as those of hyperperfusion and pulmonary hypertension. The proximal elastic arteries develop less elastin than normal, while the intra-acinar arteries are usually smaller and have a thinner coat. Pulmonary arterial thromboses can occur and they account for eccentric areas of intimal fibrosis. Moreover the development of the alveoli is impaired when the lung is severely hypoperfused.[19 20] Extrapolation of vascular resistance at a higher flow condition (that is, full systemic flow as after a Fontan operation) from a resistance calculated in a low flow condition (that is Qp/Qs < 0·7) requires some assumptions such as adequate compliance of the pulmonary vascular bed.[21] This study and other observations have led our surgeons often to prefer a shunt procedure to a Fontan operation in cyanotic patients.

A second but less frequent tachycardia noted in the early postoperative period was His bundle tachycardia. In contrast to atrial flutter this was not predicted by preoperative or postoperative haemodynamic condition. Similar arrhythmias have been seen after other cardiac operations involving manipulation of the area around the atrioventricular node, including repair of a ventricular septal defect and tetralogy of Fallot.[22] Such arrhythmias were particularly poorly tolerated in the Fontan circuit, in which only minor increases in left atrial pressure can be disastrous. Such an increase resulted in rapid deterioration and death in our patients. Presumably, His bundle tachycardia is related to some aspects of the surgery itself. The Fontan operation requires atrial manipulation and suturing, and damage to the atrioventricular node and its blood supply is one possible basis for arrhythmia. Currently our understanding of the electrophysiological basis of this less common but potentially lethal arrhythmia is limited. We are now evaluating different protocols involving early treatment with drugs, cooling of the patient, and atrioventricular sequential pacing.

Arrhythmias during intermediate follow up seemed to be related to haemodynamic condition. Interestingly, they occurred most often when treatment with diuretics was being tapered off either after the original Fontan operation or in two patients after a second operation. We could not determine whether reducing the dose more slowly would have avoided the postoperative arrhythmia. In nine of 11 patients sinus rhythm could be restored with medication. Multivariate analysis identified older age, increased right atrial size, and raised preoperative pulmonary artery pressure as risk factors for tachycardia during medium term follow up. It will be important to determine whether the incidence of arrhythmias increases with longer follow up, as in atrial repair of transposition of the great arteries,[23] and how it relates to preoperative factors such as palliation and timing of the Fontan operation. Only 32% (25/78) of our patients were followed for five years or more after operation. Our multivariate analysis indicated the incidence of supraventricular extrasystoles on ambulatory monitoring increased with time since repair. This accords with evidence from a large group treated at the Mayo Clinic which suggests that late arrhythmias may be an increasingly important complication during follow up after the Fontan operation.[11] In a retrospective study it is difficult to separate the effects of length of follow up from era of surgery and changes in management policy. We are currently prospectively studying preoperative, perioperative, and serial follow up ambulatory electrocardiographic monitoring of patients after Fontan repair.

Late tachycardias were well tolerated by most of our patients and none of the late deaths was provoked by an arrhythmia. Only one patient reported syncope in association with impaired systemic ventricular function. However, despite lack of immediate symptoms, loss of stable sinus rhythm may have adverse long term effects. We were able to study ventricular size and function in a group of patients before and during follow up after Fontan.[24] One patient who developed asymptomatic chronic atrial flutter during follow up showed a significant increase in ventricular dimensions and a decrease in contractility after the onset of arrhythmia. This contrasted with all the other patients studied in sinus rhythm who showed a decrease in dimensions and increase in contractility studied by load-independent indices of ventricular function after operation. Thus preservation and restoration of sinus rhythm or at least maintaining an acceptable ventricular rate is important for long term postoperative wellbeing.

Ambulatory electrocardiographic monitoring showed an increased incidence of atrial and ventricular extrasystoles compared with normal patients of similar age.[10] The clinical significance of this finding could not be evaluated in our study because we did not perform serial monitoring. As in previous studies of congenital heart disease, very few arrhythmias were recorded by ambulatory monitoring that had not been manifested by clinical follow up or standard serial electrocardiography. Likewise, submaximal exercise testing, while yielding interesting data on the determinants of cardiac output after Fontan,[25] provoked almost no arrhythmia. In none of our patients was the response of cardiac output to submaximal exercise testing over a physiological range limited by the inability to increase heart rate to appropriate values achieved by age matched controls. Currently, therefore, there does not seem to be an indication for prophylactic antiarrhythmic treatment based on findings of either ambulatory monitoring or exercise testing, especially bearing in mind the negative inotropic effects of most of such agents.

Based on our understanding of the Fontan circulation we may need to refine the indications for Fontan procedures, to alter the surgical technique on individual patients, or to consider other therapeutic strategies. The incidence of early and late arrhythmia has been an impetus to modify our surgical approach to the Fontan operation. In vitro and in vivo studies suggest several practical and theoretical advantages for the total cavopulmonary connection over the atriopulmonary connection in some patients.[26] In the total cavopulmonary connection blood from the cavae is channelled to the pulmonary artery, either by a graft or a composite channel made from prosthetic material and sinus venosus wall. Therefore a smaller atrial mass is exposed to a chronic increase in systemic venous pressure and the stress in the atrial wall is lower (law of Laplace). The coronary sinus is left in the low pressure chamber and surgery occurs well away from the atrioventricular node. We are currently conducting a prospective study using perioperative and follow up ambulatory monitoring to examine whether this modification will reduce the incidence of early and late arrhythmias after the Fontan operation.

Conclusions

In a consecutive series of patients undergoing a Fontan operation, perioperative tachycardias were common and associated with significant morbidity and mortality. Early atrial flutter was a marker of adverse preoperative and postoperative haemodynamic function whereas His bundle tachycardia was not. During intermediate follow up development of supraventricular arrhythmias was also associated with borderline haemodynamic condition and with increased right atrial dimensions. Late tachycardias were haemodynamically better tolerated than in the early postoperative period. Modifications of the surgical technique designed to diminish energy loss in the circulation and prevent right atrial distension and increased pressure may reduce the incidence of early and late arrhythmias.

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1 Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;26:240–8.

2 Kirklin J, Barratt-Boyes B. *Cardiac Surgery*. New York: John Wiley & Sons, 1986:866–72.

3 Bull C. Atrial and ventricular dependent circulations. In: Macartney FJ, ed. *Congenital heart disease*. Lancaster: MTP Press, 1986:35–53.

4 Ullal R, Anderson RH, Lincoln C. Mustard's operation modified to avoid dysrhythmias and pulmonary and systemic venous obstruction. *J Thorac Cardiovasc Surg* 1979; 78:431–9.

5 Gilette P, Kugler J, Garson A, Gutgesell H, Duff D, McNamara D. Mechanisms of cardiac arrhythmias after the Mustard operation for transposition of the great arteries. *Am J Cardiol* 1980;45:1225–30.

6 Boyden PA, Hoffman B. The effects of atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. *Circ Res* 1981;49:1319–31.

7 Boyden R, Tilley L, Rham T, Liu S, Fenoglio J, Wit A. Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. *Am J Cardiol* 1982;49:1896–909.

8 Porter C, Battiste C, Humes R, *et al*. Risk factors for supraventricular tachyarrhythmias after Fontan procedure for tricuspid atresia [abstract]. *Am Heart J* 1986; 112:645.

9 Choussat A, Fontan F, Besse P, Vallot F, Chauve A, Bricaud H. Selection criteria for Fontan's procedure. In: Anderson RH, Shinebourne EA, eds. *Pediatric cardiology*. Edinburgh: Churchill Livingstone, 1978:559–66.

10 Nagashima M, Matsushima M, Ogawa A, *et al*. Cardiac arrhythmias in healthy children revealed by 24 hour ambulatory ECG monitoring. *Pediatr Cardiol* 1987;8: 103–8.

11 Humes R, Porter C, Mair D, *et al*. Intermediate follow-up and predicted survival after the modified Fontan procedure for tricuspid atresia and double-inlet ventricle. *Circulation* 1987;76(suppl III):67–71.

12 Dickinson D, Wilkinson J, Anderson K, Smith A, Ho S, Anderson RH. The cardiac conduction system in situs ambiguus. *Circulation* 1979;59:879–85.

13 Ten Eick R, Singer D. Electrophysiological properties of diseased human atrium. I. Low diastolic potential and altered cellular response to potassium. *Circ Res* 1979; 44:545–57.

14 Puga F, Chiavarelli M, Hagler D. Modifications of the Fontan operation applicable to patients with left atrioventricular valve atresia or single atrioventricular valve. *Circulation* 1987;76(suppl III):53–60.

15 Matsuda H, Kawashima Y, Kishimoto H, *et al*. Problems in the modified Fontan operation for univentricular heart of the right ventricular type. *Circulation* 1987;76(suppl III):45–52.

16 Alboliras E, Porter C, Danielson G, *et al*. Results of the modified Fontan operation for congenital heart lesions in patients without preoperative sinus rhythm. *J Am Coll Cardiol* 1985;6:228–33.

17 Barber G, Di Sessa T, Child J, *et al*. Hemodynamic responses to isolated increments in heart rate by atrial pacing after a Fontan procedure. *Am Heart J* 1988; 115:837–41.

18 Juaneda E, Haworth SG. Pulmonary vascular structure in patients dying after a Fontan procedure: the lung as a risk factor. *Br Heart J* 1984;52:575–80.

19 Haworth S. Pulmonary vasculature. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology*. Edinburgh: Churchill Livingstone, 1987:148–9.

20 Rabinovitch M, Sanders S, Castaneda A, Reid L. Morphometric analysis of lung biopsy tissue in candidates for Fontan-type surgical procedures [abstract]. *Am J Cardiol* 1981;47:447.

21 Harris P, Segal N, Bishop J. The relation between pressure and flow in the pulmonary circulation in normal subjects and in patients with chronic bronchitis and mitral stenosis. *Circulation Res* 1968;2:73–83.

22 Wolff G, Talmer D. Arrhythmias following cardiac surgery. In: Roberts NK, Gelband H, eds. *Cardiac arrhythmia in the neonate, infant and child*. Norwalk: Appleton Century Crofts, 1983:268–9.

23 Flin C, Wolff G, Macdonald D II, *et al*. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. *N Engl J Med* 1984;310:1635–8.

24 Gewillig M, Lundström U, Bull C, *et al*. Impact of the Fontan operation on left ventricular size and contractility in tricuspid atresia. *Circulation* 1990;81:118–27.

25 Gewillig M, Lundström U, Wuse R, Bull C, Deanfield J. Exercise responses in patients after Fontan repair: patterns and determinants of performance. *J Am Coll Cardiol* 1990;15:1424–32.

26 De Leval M, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. *J Thorac Cardiovasc Surg* 1988;96:682–95.

Br Heart J 1992;67:80–3

Atrial flutter in the fetus and young infant: an association with accessory connections

Janice Till, Christopher Wren

Abstract

***Objective*—To highlight the association between atrial flutter and accessory connections in the fetus and young infant.**

***Design*—A retrospective review from January 1985 to January 1990.**

***Patients*—Fetuses, neonates, and young infants with atrial flutter.**

***Results*—Four fetuses and five infants presented with atrial flutter. In two fetuses and one infant sinus rhythm returned spontaneously. The other six required cardioversion. Three of them developed orthodromic atrioventricular re-entry tachycardia and each had evidence of an accessory connection.**

***Conclusions*—Because atrial flutter in the fetus and neonate is rare, the high incidence of accessory connections in this group points to a possible aetiology of "idiopathic" atrial flutter in this age group.**

Atrial flutter is an uncommon arrhythmia in the fetus, the neonate, and in infancy. Associated structural heart disease is unusual and most cases are considered to be idiopathic. In a five year period we encountered nine patients with atrial flutter presenting in fetal life or early infancy. Given the rarity of atrial flutter in this age group, the finding of accessory connections in three patients (33%) is likely to be of aetiological significance.

Patients and methods

From January 1985 to January 1990 we encountered nine patients with atrial flutter presenting in fetal life or early infancy. The diagnosis of atrial flutter in the fetus was made echocardiographically from the finding of a regular atrial tachycardia (rate 400–500 beats per minute) with atrioventricular block (generally 2 : 1).[1] The diagnosis of atrial flutter in the newborn was made in the presence of characteristic flutter waves on the surface electrocardiogram at 300-500 per minute with atrioventricular block. Evidence of pre-excitation was sought on all electrocardiograms, especially those recorded in sinus rhythm, but no provocative tests (such as vagal stimulation, intravenous adenosine, or oesophageal pacing) were used to unmask latent pre-excitation or in an attempt to induce tachycardia.

Results

Nine patients with atrial flutter were identified. The table gives their clinical characteristics. Two of the four patients presenting in utero reverted to sinus rhythm before birth and none of the four had evidence of pre-excitation on postnatal electrocardiograms. Six of seven patients with atrial flutter present at birth or soon afterwards had a sustained arrhythmia and required direct current cardioversion. There was no recurrence of flutter in any patient but three developed sustained orthodromic atrioventricular re-entry tachycardia and all three had evidence of an accessory connection.

Patient 3 was identified as having atrial flutter in utero at 36 weeks' gestation. Atrial flutter was still present at birth at term. The electrocardiogram confirmed the diagnosis of atrial flutter with an atrial rate of 420 per minute and 2 : 1 atrioventricular conduction but showed no evidence of pre-excitation (fig 1A). Atrial flutter persisted for 24 hours when direct current cardioversion was performed. A single shock of 5 J restored sinus rhythm for a few beats before sustained narrow QRS tachycardia at 300 beats per minute developed. A further shock again restored sinus rhythm transiently but tachycardia resumed almost immediately. The QRS complexes at the onset of tachycardia showed a left bundle branch block pattern. Spontaneous resolution of the bundle branch block was associated with a decrease in cycle length from 260 to 235 ms, supporting the diagnosis of atrioventricular re-entry tachycardia with a concealed left accessory pathway (fig 1B-D). Recordings in sinus rhythm showed no evidence of pre-excitation. The arrhythmia was difficult to control but was eventually suppressed by treatment with oral flecainide. There were occasional recurrences of orthodromic atrioventricular re-entry tachycardia over the first 18 months of life but no recurrence of atrial flutter.

Patient 7 was noted to have tachycardia during labour. An electrocardiogram after delivery showed atrial flutter of 400 beats per minute with variable atrioventricular block (fig 2A). The ventricular rate ranged from 160 to 190 beats per minute. The baby remained well and was treated with digoxin from nine days of age to control the ventricular rate. At 14 days of age he developed a wide QRS tachycardia with a ventricular rate of 200 per minute which was interpreted as atrial flutter with pre-excitation via an accessory connection (fig 2B). Treatment with digoxin was stopped and a direct current shock restored sinus rhythm. The electrocardiogram then showed Wolff-Parkinson-White syndrome and the pattern of pre-excitation was consistent with a left posterior accessory

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Clinical details of nine fetuses and infants with atrial flutter

Patient	*Sex*	*Age at presentation (wk)*	*Atrial rate (per min)*	*Ventricular rate (per min)*	*Maternal drugs*	*Rhythm at birth*	*Comments*
1	F	40*	420	210	Digoxin	SR	
2	F	40*	420	210	Digoxin	AFL	
3	M	40*	410	205	Digoxin	AFL	Concealed accessory pathway
4	M	40*	420	210	Digoxin	SR	
5	M	Birth	374	130–300		AFL	
6	M	Birth	400	200		AFL	
7	M	Birth	400	160–190		AFL	Wolff-Parkinson-White syndrome
8	F	Birth	300	300		AFL	
9	F	7 wk	360	180		?	Wolff-Parkinson-White syndrome

*Diagnosed in utero.
SR, sinus rhythm; AFL, atrial flutter.

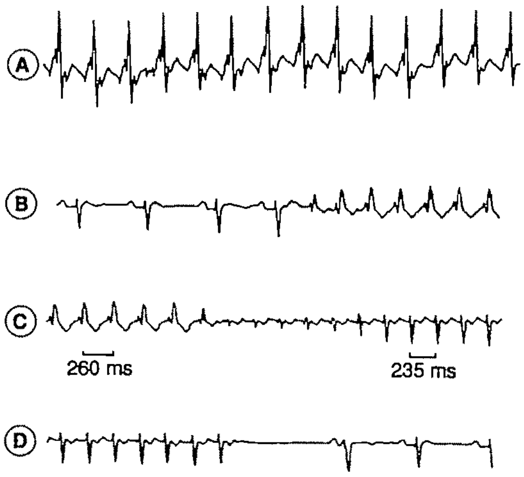

Figure 1 Electrocardiograms from patient 3. Recordings show atrial flutter with 2 : 1 atrioventricular conduction (A), onset of tachycardia with left bundle branch block pattern (B), resolution of bundle branch block with shortening of tachycardia cycle length (C), and termination of tachycardia with no evidence of pre-excitation in sinus rhythm (D). Panel A is lead I and Panels B, C, and D are lead II.

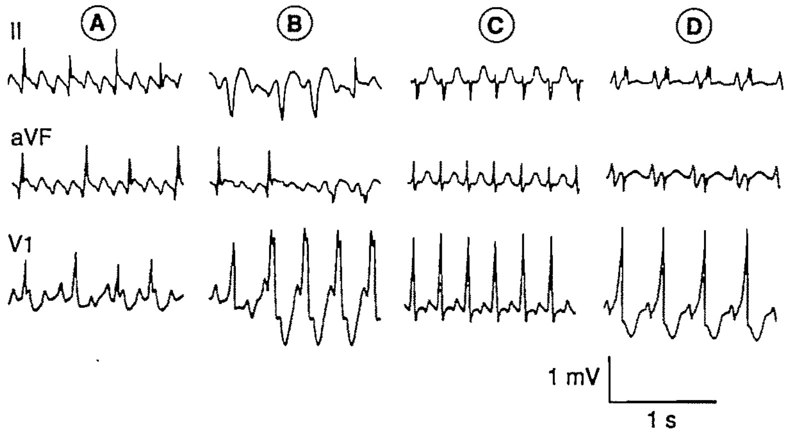

Figure 2 Electrocardiograms from patient 7. Leads II, aVF, and V1 are shown with recordings at birth (A), after treatment with digoxin showing pre-excitation (B), in orthodromic atrioventricular re-entry tachycardia (C), and in sinus rhythm showing evidence of Wolff-Parkinson-White syndrome (D).

orthdromic atrioventricular re-entry with a narrow QRS over the next 12 hours were terminated with intravenous adenosine (fig 2C). Initially tachycardia was suppressed with oral flecainide but after 36 hours incessant atrioventricular re-entry at 214 beats per minute developed. Flecainide was stopped and replaced by amiodarone. There has been no recurrence of atrioventricular tachycardia nor of atrial flutter on this treatment.

Patient 9 presented aged seven weeks with heart failure. She had had symptoms from birth and her weight had fallen from the 97th centile to the 3rd, so that at presentation she was below her birth weight. An electrocardiogram showed atrial flutter with 2 : 1 conduction (fig 3A). Observation showed intermittent pre-excitation with a delta wave present for about 30 seconds (fig 3B) followed by normal conduction for 30 seconds. Electrical cardioversion restored sinus rhythm and the electrocardiogram then showed a delta wave with the pattern of pre-excitation suggesting a posteroseptal accessory pathway (fig 3D). Within 15 minutes the baby developed a narrow QRS tachycardia at 300 per minute (fig 3C). Adenosine restored sinus rhythm on three occasions and the fourth episode was treated with intravenous flecainide. This was followed by oral flecainide and there has been no recurrence of atrial flutter or orthodromic atrioventricular re-entry in 12 months of follow-up.

Discussion

Sustained tachycardia in the newborn is uncommon and at this stage atrial flutter occurs much less frequently than supraventricular tachycardia. Both arrhythmias also occur in the fetus but flutter is then proportionately more common.[2] Compared with older children very few fetuses or infants with atrial flutter have associated structural heart disease and the arrhythmia is usually considered to be idiopathic.[3] The three cases we describe showed the typical electrocardiographic features of atrial flutter in this age group. The new born atria differ from those in the adult in their ability to sustain high flutter rates which may exceed 400 per minute.

The presence of accessory connections in three of our nine patients, all with sustained atrioventricular re-entry tachycardia after treatment of the atrial flutter, is intriguing and is likely to be of aetiological importance. The association of atrial flutter and accessory connections in the fetus and the newborn has been reported occasionally but its significance has probably not been fully appreciated. Lubbers *et al* reported eight infants with atrial flutter, two of whom had Wolff-Parkinson-White syndrome.[4] Rowland *et al* reported seven cases of atrial flutter (two in the fetus and five in the newborn) with one case of recurrent paroxysmal supraventricular tachycardia probably due to an accessory connection.[5] Chantepie *et al* documented atrial flutter, rapid atrial tachycardia, and orthodromic atrioventricular re-entry tachycardia in a premature baby with Wolff-Parkinson-White syndrome.[6] Belhassen *et al* described a baby with Wolff-Parkinson-White

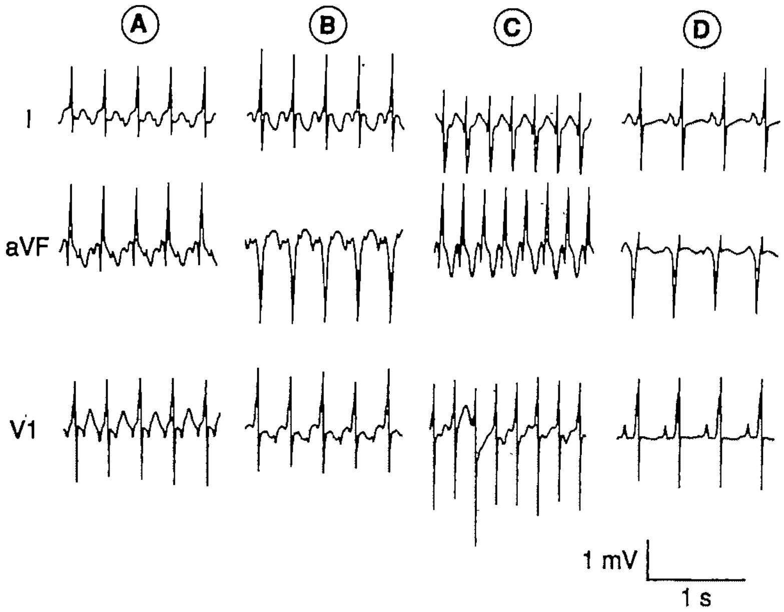

Figure 3 Electrocardiograms from patient 9. Leads I, aVF, and V1 are shown. Recordings were taken at presentation in atrial flutter with 2 : 1 atrioventricular conduction without (A) and with pre-excitation (B), after cardioversion showing orthodromic atrioventricular re-entry tachycardia (C), and in sinus rhythm showing evidence of Wolff-Parkinson-White syndrome (D).

syndrome and atrial flutter documented in utero and postnatally.[7] Meha *et al* described a baby born at 36 weeks' gestation by emergency caesarean section for fetal tachycardia.[8] They observed atrial flutter with intermittent 1 : 1 anterograde conduction over an accessory connection and "atrial fibrillation", which in retrospect seems more likely to have been atrial flutter with variable atrioventricular block after the administration of digoxin, lignocaine and phenytoin. Johnson *et al* reported a case in which fetal supraventricular tachycardia at 26 weeks' and atrial flutter at 27 weeks' gestation were confirmed echocardiographically.[9] Sinus rhythm resumed after maternal treatment with quinidine. A postnatal tranoesophageal electrophysiological study confirmed the presence of a left lateral accessory connection. Maxwell *et al* described 23 cases of fetal tachycardia; 12 supraventricuar tachycardia, eight atrial flutter, and three in which the rhythm varied between supraventricular tachycardia and atrial flutter.[2] No details of the postnatal electrocardiograms were given. Deal *et al*, in a report of 90 infants with Wolff-Parkinson-White syndrome, found one born with atrial flutter who developed a wide QRS tachycardia on digoxin, similar to patient 7 in our series.[10] Dunnigan *et al*, Martin and Hernandez, and Moller *et al* between them reported 24 cases of atrial flutter with no evidence of accessory connections.[11-13]

The underlying cause of atrial flutter in the fetus and the newborn is unknown. The association of atrial flutter and atrioventricular re-entry tachycardia via an accessory connection in our cases and in the reports above is interesting and may be of aetiological importance, given the rarity of atrial flutter in this situation. In adults the association between atrial flutter and accessory connection arrhythmias is well recognised. Episodes of sustained atrioventricular re-entry tachycardia have been reported to revert directly to atrial flutter.[14] The occurrence of atrial flutter in the fetus or the neonate with an accessory connection may represent a similar phenomenon. The reason for the degeneration of atrioventricular re-entry tachycardia into atrial flutter or fibrillation is not clear but the occurrence of an atrial extra-stimulus during the atrial vulnerable period may play a part. Atrioventricular re-entry tachycardia in the fetus or newborn often impairs cardiac function and may cause appreciable atrial dilatation. This may facilitate the initiation and maintenance of atrial flutter which, with its shorter cycle length, would then become the dominant rhythm. A further theoretical mechanism is the possible retrograde conduction of ventricular extrasystoles to the atrium via the accessory connection which might initiate atrial flutter.[15]

The electrophysiological characteristics of the heart change rapidly from the fetus to the neonate and during the first year of life, although the full extent of these changes is unknown. The different rates of atrioventricular re-entry tachycardia in the fetus and the neonate are well recognised, as are changes with age in the conduction characteristics and refractory periods of accessory pathways.[16,17] Such changes may underlie the difference in the relative incidence of atrial flutter and atrioventricular re-entry tachycardia in the fetus, the neonate, and the infant and may explain the dramatic reduction in the occurrence of isolated atrial flutter with increasing age and maturity in early life. Cessation of spontaneous recurrences of supraventricular tachycardia and of pre-excitation in the newborn with Wolff-Parkinson-White syndrome is common.[18] Disappearance, whether functional or physical, of accessory connections during fetal life is probably also common, so that there may be no evidence of an accessory connection once sinus rhythm is restored after birth.

This association may have implications for management. Historically digoxin has been used as the drug of first choice for flutter in young children.[5,13] The action of digoxin on atrial cells is to shorten the refractory period, an action which theoretically would enhance the chances of atrial flutter being sustained rather than bring about its termination, although it may decrease the ventricular rate by slowing atrioventricular node conduction. The use of digoxin in atrial flutter with an accessory connection is more controversial as it is known that digoxin may decrease the anterograde refractory period of the accessory connection, thus allowing more atrial impulses to reach the ventricle—a potentially life-threatening situation. We feel, therefore, that digoxin should not be the drug of first choice in this situation and recommend direct current cardioversion or overdrive atrial pacing in preference.

1 Allan LD, Anderson RH, Sullivan ID, Campbell S, Holt DW, Tynan M. Evaluation of fetal arrhythmias by echocardiography. *Br Heart J* 1983;50:240–5.
2 Maxwell DJ, Crawford D, Curry PVM, Tynan MJ, Allan LD. Obstetric importance, diagnosis, and management of

fetal tachycardias. *BMJ* 1988;297:107–10.

3 Garson A, Bink-Boelkens M, Hesslein PS, Hordof AJ, Keane KF, Neches WH, *et al*. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol* 1985;6:871–8.

4 Lubbers WJ, Losekoot TG, Anderson RH, Wellens HJJ. Paroxysmal supraventricular tachycardia in infancy and childhood. *Eur J Cardiol* 1974;2:91–9.

5 Rowland TW, Matthew R, Chameides L, Keane JF. Idiopathic atrial flutter in infancy: a review of eight cases. *Pediatrics* 1978;61:52–6.

6 Chantepie A, Ramponi N, Vaillant MC, Laugier J, Raynaud P, Fauchier JP. Tachycardie auriculaire polymorphe et syndrome de Wolff-Parkinson-White chez le nouveau-né. *Arch Mal Coeur* 1986;9:1371–5.

7 Belhassen B, Pauzner D, Blieden L, Sherez J, Zinger A, David M, *et al* Intrauterine and postnatal atrial fibrillation in the Wolff-Parkinson-White syndrome. *Circulation* 1982;66:1124–8.

8 Mehta AV, Pickoff AS, Raptoulis A, Wolff GS, Garcia OL, Tamer DF, *et al* Atrial flutter and atrial fibrillation associated with Wolff-Parkinson-White syndrome in childhood. *Pediatr Cardiol* 1980;1:197–202.

9 Johnson WH, Dunnigan A, Fehr P, Benson DW. Association of atrial flutter with orthodromic reciprocating fetal tachycardia. *Am J Cardiol* 1987;59:374–5.

10 Deal BJ, Keane JF, Gillette PC, Garson A Jr. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up. *J Am Coll Cardiol* 1985;5:130–5.

11 Dunnigan A, Benson DW Jr, Benditt DG. Atrial flutter in infancy: diagnosis, clinical features and treatment. *Pediatrics* 1985;75:725–9.

12 Martin TC, Hernandez A. Atrial flutter in infancy. *Pediatrics* 1982;100:239–41.

13 Moller JH, Davachi F, Anderson RC. Atrial flutter in infancy. *J Pediatr* 1969;75:643–51.

14 Sung RJ, Castellanos A, Mallon SM, Bloom MG, Gelband H, Myerberg RJ. Mechanisms of spontaneous alteration between reciprocating tachycardia and atrial flutter—fibrillation in the Wolff-Parkinson-White syndrome. *Circulation* 1977;56:409–16.

15 Fujimura O, Klein GJ, Yee R, Sharma AD. Mode of onset of atrial fibrillation in the Wolff-Parkinson-White syndrome: how important is the accessory pathway? *J Am Coll Cardiol* 1990;15:1082–6.

16 Zales VR, Dunnigan A, Benson DW Jr. Clinical and electrophysiologic features of fetal and neonatal paroxysmal atrial tachycardia resulting in congestive heart failure. *Am J Cardiol* 1988;62:225–8.

17 Benson DW Jr, Dunnigan A, Benditt DG. Follow-up evaluation of infant paroxysmal atrial tachycardia: transesophageal study. *Circulation* 1987;75:542–9.

18 Dunnigan A, Benditt DG, Benson DW Jr. Modes of onset ("initiating events") for paroxysmal atrial tachycardia in infants and children. *Am J Cardiol* 1986;57:1280–7.

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Normal relation between heart rate and cardiac repolarisation in sudden infant death syndrome

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Abstract

Objective—**To determine whether there was a difference in the relation between heart rate and RT intervals in infants who later died of sudden infant death syndrome (SIDS) and controls.**

Design—**A blinded, computer analysis of prospectively acquired physiological data on SIDS cases and controls.**

Setting—**Physiological data obtained from infants at home (collaborative analysis National Heart and Lung Institute and Exeter University).**

Participants—**Nine fullterm infants who subsequently died of SIDS and 10 surviving controls matched for age and birth weight.**

Interventions—**24 hour tape recordings of the electrocardiogram at home between three and 11 weeks of age.**

Main outcome measures—**Mean value of the constant b, which relates by linear regression the log of each RT interval to the log of its preceding RR interval, and any difference between SIDS cases and controls.**

Results—**The mean (2SEM) values for b were 0·20 (0·03) for the 10 controls and 0·19 (0·03) for the nine SIDS infants. Cyclical correlations between RT and RR intervals of varying strength were identified in both SIDS infants and controls.**

Conclusions—**Infants who subsequently died of SIDS did not show an impaired ability to modify RT intervals in response to change in heart rate.**

In our previous prospective studies of electrocardiograms from infants who died of sudden infant death syndrome (SIDS) we did not find any predictive lengthening of the QT interval.[1,2] The purpose of this present analysis was to evaluate the response of the QT interval to variations in heart rate. We hypothesised that a defect in this response might indicate a vulnerability to dangerous ventricular arrhythmias. A similar analysis has been reported by Sadeh *et al*[3] of 24 hour electrocardiographic recordings collected by us[1] from 10 infants who subsequently died of SIDS. The ability to shorten their QT interval in response to an increasing heart rate was reported to be impaired in five of their 10 cases. As a result of their findings Sadeh *et al* argued that "sudden death in these cases may have resulted from defective modulation of cardiac repolarisation".[3] In contrast our own analysis of the same data has produced different results. In the light of potentially harmful preventive therapies, we consider it important to describe our own analysis. We then discuss the possible reasons for this evident conflict between our findings and those of Sadeh *et al.*[3]

Patients and methods

We analysed segments from ten 24-hour cassette tape recordings of electrocardiograms obtained prospectively on nine full term victims of SIDS aged 16–63 days at the time of recording (birth weights from 2·35 to 4·79 kg) (table 1). Ten similar recordings on 10 surviving fullterm controls matched for postnatal age (21–75 days) and birth weight (2·64–4·00 kg) were similarly studied (table 1). We examined the same recordings from SIDS cases as Sadeh *et al.*[5] However, Sadeh *et al* included only data from midnight to 6 am; we intentionally used complete data from the entire *24 hour period* to include daytime and night time activity.

The waveforms in the prospective study yielding these data[1] were obtained from two electrodes on the chest wall. The frequency content of the resulting signals was 0·5–70 Hz after processing through the tape replay system (Oxford Medilog PB2). Details of the technique have been previously reported in detail.[4,5] In brief, electrocardiograms from the Medilog recorder together with the simultaneously recorded 60 Hz calibration signals were

Table Details of recordings and infants

Age (days)	*Birth weight (g)*	*Gestation (wk)*
	SIDS cases	
16	2780	39
24*	3770	40
63*	3770	40
30	2350	40
40	3030	40
40	3960	41
41	4790	40
47	2920	40
52	2810	39
61	2980	40
	Controls	
21	3660	42
36	3700	42
75	2640	38
37	3740	38
39	3690	40
42	3300	40
42	3230	39
42	3950	40
55	3800	40
61	4000	38

*Same infant.

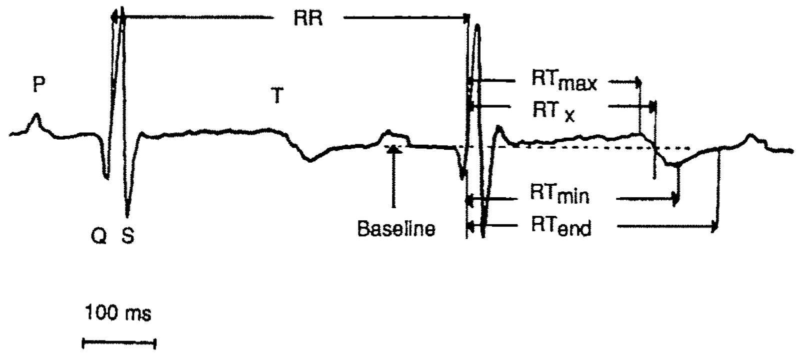

Figure 1 An example of two electrocardiographic complexes from one of the controls. RT_{max}, RT_x, RT_{min} and RT_{end} behave in a similar fashion to the QT interval with changes in the immediately preceding RR interval. RT_x was chosen to represent ventricular repolarisation time.

played back from an FM tape recorder at real time speed (SE Labs 8-4, frequency response DC to 625 Hz). Sections of the original tape recordings were chosen to cover as wide a range of RR intervals as possible in every subject. Any fluctuations in the tape speed produced by the tape recorders or their tape replay system were detected and compensated by a specially made correction device.[6] Slowed down re-recordings were digitised at approximately 4 kHz, the sampling rate being dependent on the frequency of the calibration signal. Waveforms were analysed by a microprocessor-based computer system.

Each RR interval was measured from the rapidly rising part of the R wave at a level just above that of the height of the P wave. We obtained a baseline from which to make measurement of ventricular repolarisation time (RT interval) by averaging 64 data points from the flat portion of the PR interval. The Q wave was not included, preference being given to the more consistent and sharper R wave deflection. Measurements were made (fig 1) of the times from the rapidly rising part of the R wave to (*a*) the point of maximum amplitude of the T wave (RT_{max}), (*b*) the point where the T wave crossed the baseline value (RT_x), (*c*) the point of minimum amplitude of the T wave (RT_{min}), and (*d*) the point where the T wave crosses the baseline again (RT_{end}). Previous investigations have shown that all four measurements vary in similar fashion with changes in the RR interval.[4,5] The similarity between the four measurements existed over the full range of RR intervals. However, these latter studies also showed that the random variations in the RT_x intervals were much reduced compared with those of the remaining three measurements. The RT_x interval also had the advantage of being less affected by those electrocardiographic waves that were so short that the P wave was mixed in with the end of the T wave.

The small size of the QR interval and the close relation between changes in the preceding RR intervals and both RT_x and RT_{end} indicated that a good estimate of the relation between QT and RR intervals could be obtained by assuming that QT interval duration is directly proportional to RT_x. (Linear regression analysis was used to fit equations to plots of RT_{end} against RR and plots of RT_x against RR from data obtained in the previously reported study.[4,5] The mean (SEM) slopes and intercepts respectively were 0·35 (0·03) and 57 (12) ms for RT_x against RR and 0·37 (0·03) and 70 (12) ms for RT_{end} against RR).

If it is assumed that RT_x and QT are directly proportional the following equation can be written:

$$\log_e(RT_x) = b \log_e(RR) + k \quad \textit{equation 1}$$

where k is the intercept and where b is a constant that relates the RT_x to the RR according to a power law.

From each 24 hour tape recording of SIDS cases and controls, a technician who did not know whether the data originated from a SIDS case or a control selected 8–10 segments using the data collected in the earlier study.[4,5] Each segment consisted of 63 consecutive cardiac cycles with a high signal to noise ratio. The number of segments was chosen to ensure statistical significance for each measurement of b and k. The number of cardiac cycles per segment (63) was chosen to match the program within the eight-bit microprocessor and was consistently large enough to include several short-term cycles in heart rate variability. The segments from each infant, whether a control or SIDS case, were chosen so as to provide as wide and evenly spaced a range of RR intervals as possible. The computer data were in the form of approximately 1000 numerical tables, each table consisting of 63 pairs of consecutive RR and RT_x values. Only those tables that showed no trace of artefact (low noise) when observed on an oscilloscope as they were being loaded into the computer were selected by the independent technician.

The RR interval range for each of the segments of 63 heart beats in the controls varied from 14 to 288 ms; that is, in one segment the RR interval varied by only 14 ms over the 63 beats while at the other extreme the RR interval varied by 288 ms over the 63 beats. The overall range for the SIDS cases varied from 8 to 294 ms.

Correlation coefficients and values of b were obtained by fitting equation 1 to the RT_x values and their corresponding RR values by linear regression analysis for both SIDS cases and controls (fig 2A, B, and C). These values of b were also plotted against the individual ranges of RR intervals within each 63 beat segment for all recordings in both controls and SIDS cases (fig 3). Time series plots of successive RR and RT_x intervals were then obtained for each 63 beat segment analysed.

Results

The mean (2 SEM) value of b for the SIDS cases was 0·20 (0·02) when all 10 SIDS recordings were used and 0·19 (0·03) when analysis was limited to the later of two recordings on one of the SIDS cases. For the surviving controls the mean value of b was 0·20 (0·03). The time series plots of RR and RT_x intervals behaved in

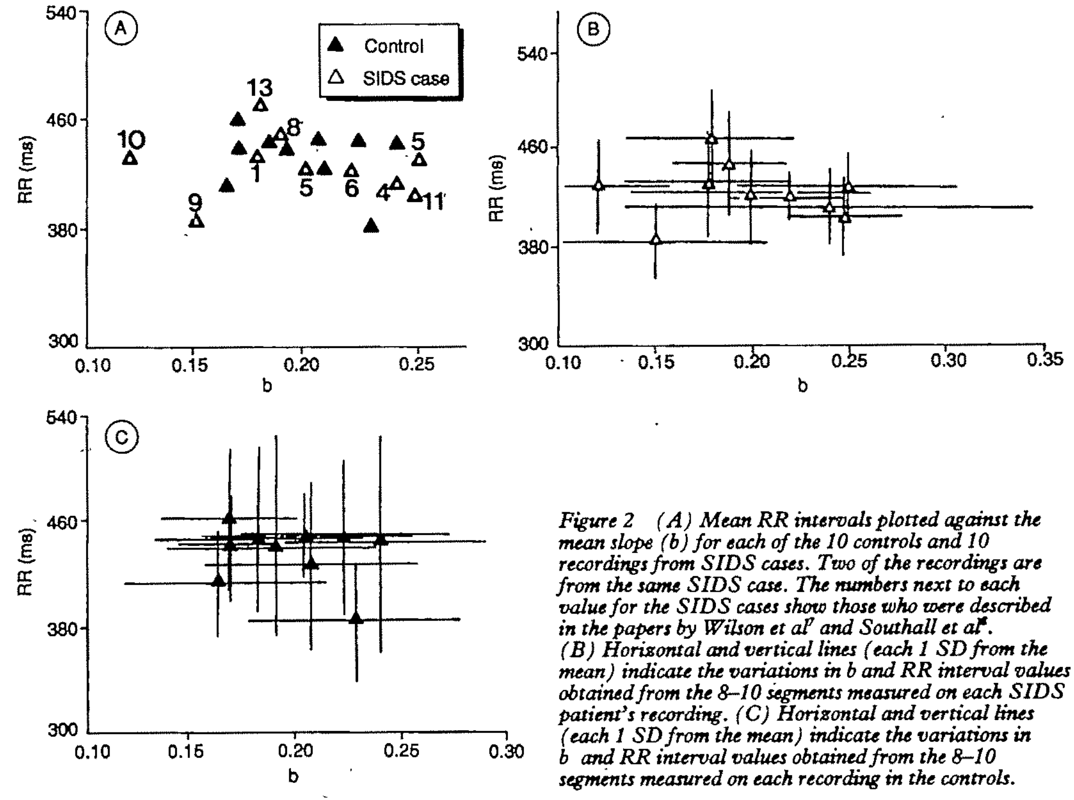

Figure 2 (A) Mean RR intervals plotted against the mean slope (b) for each of the 10 controls and 10 recordings from SIDS cases. Two of the recordings are from the same SIDS case. The numbers next to each value for the SIDS cases show those who were described in the papers by Wilson et al[7] and Southall et al[8]. (B) Horizontal and vertical lines (each 1 SD from the mean) indicate the variations in b and RR interval values obtained from the 8–10 segments measured on each SIDS patient's recording. (C) Horizontal and vertical lines (each 1 SD from the mean) indicate the variations in b and RR interval values obtained from the 8–10 segments measured on each recording in the controls.

such a similar fashion for both controls and SIDS cases that they could not be distinguished by statistical analysis. Periodicities of varying amplitude and correlation were frequently seen in the different segments from each infant, irrespective of whether they were victims or controls. Figure 2A shows the data for the nine cases of SIDS (10 recordings) and 10 controls, constructed by plotting the mean RR interval for all segments on each infant against the mean value of b for the same segments. The numbers set against the SIDS patients indicate those infants in whom heart rate[7] and heart rate variability[8] were measured in earlier studies. Figure 2A clearly shows that it is not possible to distinguish SIDS cases from their controls by the value of b. The range of the mean values of b in both SIDS cases and controls is 0·11 to 0·25.

Figure 2B shows the variability in terms of standard deviation from the mean for the values of both b and RR intervals for all recorded segments from infants dying suddenly. Values in the controls were virtually identical (fig 2C).

Figure 3 shows the mean values of b for both SIDS cases and controls plotted against the mean RR interval ranges. The mean value of b for the RR range of 212 ms is the mean of seven points. All the other mean values have been calculated by grouping the values of b and their respective RR ranges into sets of at least 10. There was no significant difference between the SIDS group and the controls in this graph. As the range of RR intervals increased the value of b fell.

Cyclical behaviour in the relation between RT and RR intervals was as common in the controls as in the SIDS cases.

Discussion

Prospective identification of infants at risk of sudden death is a desirable objective on which to base preventive care. However, incorrect predictors may prompt harmful intervention, especially if cardioactive treatment is being considered. This is why the results presented by Sadeh *et al*,[3] with their implications concerning prediction, must be confirmed or rejected. Unfortunately, only one prospective data base is available on which these results can be checked and that is the original 24 hour electrocardiograms obtained by our group.[1] Sadeh *et al's* report was published before we

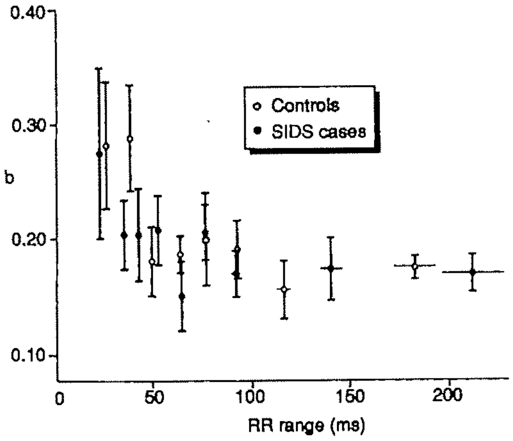

Figure 3 Plot of mean values of b for both SIDS cases and controls against the mean RR interval ranges. The value of b at the RR interval range of 212 ms is the mean of seven points. All of the other mean values were calculated by grouping the values of b and their respective RR ranges into sets of at least 10. The horizontal and vertical lines are SEMs.

had completed an analysis of our data with exacting attention to several technical and mathematical artefacts that could easily invalidate conclusions about the association between ventricular electrical activity and the incidence of sudden infant death. This analysis is now complete and unlike Sadeh *et al* we found no consistent differences between SIDS cases and controls.

The analysis in this paper differs from that carried out previously by our group.[4 5] Earlier work was based on mean values of the intervals in the electrocardiogram obtained by simply averaging over 63 consecutive heart beats. In the present study we undertook the more difficult investigation of the relation between individual RT ventricular repolarisation times and each preceding RR interval (fig 1).

This analysis of the time-series relation between RT and RR intervals did not show any difference between recordings from SIDS infants and their surviving controls. These results do not, therefore, support the hypothesis that a disordered relation, as measured from the surface electrocardiogram, between ventricular repolarisation time and heart rate influences subsequent sudden unexplained infant death. Moreover, within each infant's recording, whether they were SIDS cases or controls, some segments were found to show a strong cyclical correlation between RT and RR intervals while others showed no such relation. Sadeh *et al* inferred that unlike SIDS cases the controls always showed this strong correlation.

The spread of values for the constant b (which relates by linear regression the log of each RT interval to the log of its preceding RR interval) in both controls and SIDS cases in this present study was less (0·11–0·25) and the mean value of b for controls was greater (0·20) than values found by Sadeh *et al*[3] (their range was 0·05–0·25, and their mean for controls was 0·13). These present findings, however, do accord with those of Sadeh *et al*[3] in suggesting that Bazett's formula[9] (where b = 0·50) provides an inappropriate method for correcting the QT interval for heart rate in this age group.

The following differences between SIDS cases and controls were reported by Sadeh *et al.*[3] Firstly, according to the equation $QT = C(RR)^b$, their mean (1 SD) values for b were 0·096 (0·032) in the SIDS cases and 0·134 (0·043) in controls ($p < 0·02$). Secondly, their illustrated time series of QT intervals plotted against the immediately preceding RR intervals from 500 consecutive heart beats showed, in a single control recording, highly correlated cyclical variations in both intervals. There was a much smaller correlation in a similar plot from a single time series from a SIDS case. Presumably these two plots were included to lend weight to differences that they concluded existed between the controls and five of the SIDS subjects. Finally, in their plot of b against mean RR intervals for each segment of the recording analysed for the 10 SIDS cases and 29 controls, five of the 10 sudden death values for b fell outside the 95% confidence interval for the controls.

There are several possible explanations for the differences between our results and those of Sadeh *et al.*[3] Firstly, to "improve the reliability of their statistical comparisons" Sadeh *et al*[3] selected their segments on the basis that the RR intervals within each segment varied by more than 100 ms. As shown in fig 3, this could result in lower values of b. If values of b in this present report are limited to those segments where the RR interval range is > 100 ms (> 45 sets of points), mean (2 SEM) values of b are 0·16 (0·03) for controls and 0·17 (0·02) for SIDS cases. These values are reasonably close to the control measurements of Sadeh *et al*[3] (0·13 (0·04) (SD)). The small remaining difference between the control values of b is possibly a result of the two different methods by which each study chose to compensate for the difficulties in estimating the end of ventricular repolarisation. A second possible explanation for the different results is the high pass (10 Hz cut-off) filter used by Sadeh *et al*[3] before the measurement of QT and RR intervals. This filter produces a phase difference between input and output signals which decreases as the frequency components of the input signal increase. Therefore, with higher heart rates containing correspondingly higher frequencies, there would be a smaller timing error between the true QT and their measured QT interval. This would result in the changes in duration of the QT interval appearing to be smaller in response to changes in RR interval at the higher heart rates. For this reason we did not use a highpass filter but rather a high quality frequency modulated tape copy directly from the original 24 hour cassette recordings. Contrary to the statement made by Sadeh *et al*,[3] the frequency response of the signals after replay through the Oxford Medilog PB2 system is 0·5–70 Hz not 10–100 Hz. Nevertheless, as previously reported by us,[1] the frequency response of the original cassette tape recording system is not ideal for low frequency signals such as the T wave (diagnostic electrocardiogram recordings have bandwidths from 0·05 to 100 Hz).

A third reason for the discrepancy between these present results and those of Sadeh *et al*[3] concerns the comparability of heart rates analysed in the SIDS cases and their controls. Figure 5 of their study showed that the five recordings from SIDS cases that showed the lowest values for b also had higher average heart rates than controls. In the present study we compensated for the significantly higher heart rates previously reported to be present in these particular recordings from SIDS cases[7 8] by selecting segments in both controls and SIDS cases where the range of heart rates was as wide as possible (for example, by including data from the whole 24 hour period) and by matching our controls for birth weight and postnatal age.

Sadeh *et al* reported a linear relation "significantly different from zero at P = 0·0002" for their plot of mean RR intervals against mean values of b in their control group.[3] In our analysis no such linear relation was seen between mean b and mean RR for our controls (see fig 2A), thus supporting our use of a power equation. It is difficult to understand how Sadeh *et al*[3] can reconcile their findings of a linear relation and continue to use the original power law equation where b is assumed to be constant with respect to RR.

In conclusion, as in our earlier reports,[1 2] we found no evidence to support the hypothesis that a defect in ventricular repolarisation time or its relation to heart rate are predictive for sudden and unexplained infant deaths. We can rule out neither the unlikely possibility that a serious repolarisation abnormality was present that could not be detected by surface electrocardiogram nor the possibility that a subsequent defect in repolarisation developed closer to the time of death.

We thank Mrs Joyce Lamb for her help in preparing these data for analysis, Dr A J Wilson for his early suggestions on apparent heart rate effects on QT intervals resulting from the inherent phase response of high pass filters, and to Dr W New and Professor R H Anderson for their expert advice on this paper.

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1 Southall DP, Richards JM, de Swiet M, Arrowsmith WA, Cree JE, Fleming PJ, *et al.* Identification of infants destined to die unexpectedly during infancy: evaluation of predictive importance of prolonged apnoea and disorders of cardiac rhythm or conduction. First report of a multicentred prospective study into the sudden infant death syndrome. *BMJ* 1983;286:1092–6.
2 Southall DP, Arrowsmith WA, Stebbens V, Alexander JR. QT interval measurements before sudden infant death syndrome. *Arch Dis Child* 1986;61:327–33.
3 Sadeh D, Shannon DC, Abboud S, Saul JP, Akselrod S, Cohen RJ. Altered cardiac repolarization in some victims of sudden infant death syndrome. *N Engl J Med* 1987; 317:1501–5.
4 Wynn VT. Heart rate dependence of the RT interval in the first month of life. *Clin Phys Physiol Meas* 1986;7:369–73.
5 Wynn VT. Measurement and analysis of RT and RR intervals in 72 infants in the age range 2 to 75 days. In: Copeland K, ed. *Progress reports on electronics in medicine and biology*. The Institution of Electronic and Radio Engineers, 1986:331–6. ISBN 0903748657.
6 Bundy K, Wynn VT. ECG tape-speed error compensator. *Med Biol Eng Comput* 1985;23:607–9.
7 Wilson AJ, Stevens V, Franks CI, Alexander JR, Southall DP. Respiratory and heart rate patterns in infants destined to die of the sudden infant death syndrome. *BMJ* 1984;290:497–501.
8 Southall DP, Stevens V, Franks CI, Newcombe RG, Wilson AJ. Sinus tachycardia in term infants preceding sudden infant death syndrome. *Eur J Pediatr* 1987;147:74–8.
9 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–70.

Atrial myxoma: a tumour in search of its origins

D M Krikler, J Rode, M J Davies, N Woolf, Eileen Moss

Abstract

***Objective*—To determine whether atrial myxomas express antigens suggesting a neural origin.**

***Design*—A retrospective analysis based on immunohistochemical examination of myxoma tissue.**

***Setting*—Atrial myxomas excised by two tertiary referral cardiothoracic surgical units.**

***Subjects*—24 excised atrial myxomas. Three were from known cases of familial myxoma syndrome.**

***Methods*—Immunohistochemical identifications of three neuroendocrine markers (protein gene product (PGP) 9·5, neurone specific enolase (NSE), synaptophysin) and S100 antigen; CD34 and von Willebrand factor; and α smooth muscle actin to identify possible Schwann cell differentiation, endothelial cells, and smooth muscle cells respectively.**

***Results*—The myxoma cells were PGP 9·5 positive in 18, S100 positive in 16, and NSE positive in 12. Of the 12 NSE positive myxomas seven were synaptophysin positive. All tumours that were NSE positive were also S100 and PGP 9·5 positive. The tumour surface was partially covered by myxoma cells, partly by endothelial cells.**

***Conclusion*—The histological appearances of myxomas with stellate cells embedded within a loose connective tissue stroma, abundant basophil cell infiltration, and the presence of pericellular type IV collagen are similar to nerve sheath tumours (neurofibromas) at other sites. A significant proportion of myxomas also express Schwann cell and neuroendocrine differentiation markers. These features cannot prove the origin of myxomas because tumours may develop aberrant phenotype expression but they do accord with the view that myxomas originate from endocardial sensory nerve tissue.**

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Atrial myxomas arouse considerable clinical interest, their protean presenting features being described in numerous case reports. The chromosomal characteristics of atrial myxomas suggest that they are neoplasms rather than simply organised thrombi[1] but their exact origin is controversial.

The morphological features of myxomas are highly characteristic but not immediately reminiscent of tumours in other tissues or organs. Myxomas project into the atrial cavity and have a stalk or base incorporated into the endocardium. The lesion can be peeled away from the underlying myocardium from which there is no obvious evidence of an origin. The tumour consists of a myxoid stroma in which are embedded single stellate cells in addition to larger clumps of similar cells often arranged as a collar around open spaces. Types I and III collagen are present in small amounts only but there is a diffuse reticular stroma with fine collagen fibrils on which iron encrustation often occurs. Type IV collagen is present around clumps of myxoma cells. The stroma is very rich in connective tissue mucins and contains large numbers of plasma and mast cells. The stromal stellate cells are regarded as the essential neoplastic element; one view is that they originate in an undifferentiated endocardial connective tissue cell. Nests of such cells around the rim of the fossa ovalis[2] would explain the predilection of myxomas for this site. This view takes little account either of the histological structure of the tumour or of some interesting clinical correlations. One of us (DK) spotted one report of a myxoma that produced vasointestinal peptide,[3] and another that familial atrial myxomas were associated with lentiginosis, cutaneous neurofibromas, blue naevi and phaeochromyocytomas as well as endocrine tumours in the pituitary and testes.[4] These associations prompted DK to question whether atrial myxomas have a potential to produce tumours with neuroendocrine differentiation also whether they have affinity with neurofibromas.

Immunohistochemical techniques can be used to identify specific antigens expressed on tumour cells within the tissue and to define phenotypic expression. We have used markers for neural and neuroendocrine differentiation to study a series of myxomas.

Materials and methods

Twenty four atrial myxomas were studied; three of these were known to be familial. The following primary antibodies were used on paraffin embedded sections after tissue fixation in formol saline: protein gene product 9·5 (Ultraclone), neurone specific enolase (ICN Biomedicals), S100 (Dakopaths), synaptophysin 38 (Boehringer), von Willebrand factor (Dakopaths), CD34 (Q BEND/10 Serotec), and α smooth muscle actin (Sigma).

Where single antibody staining was used

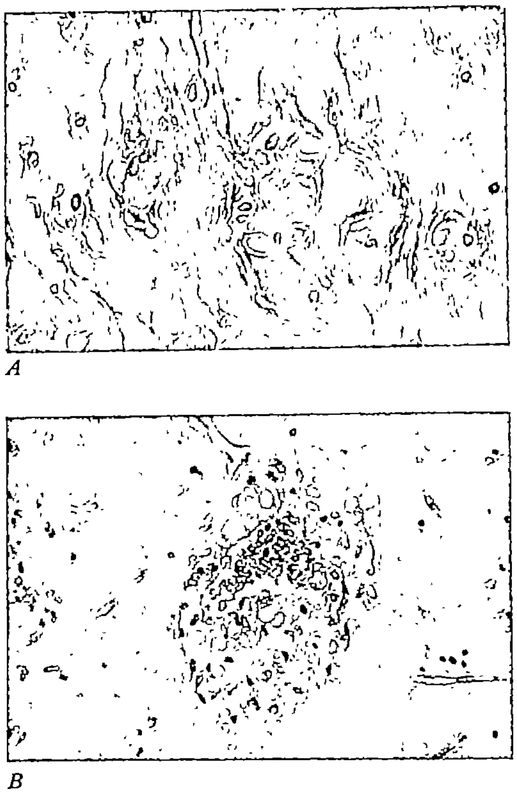

Figure 1 Haematoxylin and eosin stained sections of atrial myxoma. (A) Small clumps and single myxoma cells embedded in an amorphous stroma that is partly stained blue (basophilia) and partly pink (eosinophilia). (B) A vascular space containing red cells surrounded by a mantle of myxoma cells.

the alkaline phosphatase and monoclonal antialkaline phosphatase (APAAP) technique[5] was used to identify specific binding. In double antibody studies the first antigen was visualised by the immunoperoxidase ABC method and the second antibody by the APAAP method. Positive (known positive tissues—that is, islet cell tumours) and negative (omission of primary antibody) controls were included in each staining run.

PGP 9·5 (molecular weight 27 000) is a soluble protein extracted originally from brain tissue[6] and present in neurones, nerve axons, and neuroendocrine cell types in normal tissues. Neurone specific enolase[7 8] is a separate cytoplasmic soluble protein found in axons. S100 protein is found in both Schwann cells and melanocytes in normal human tissue.[9] Synoptophysin is a glycoprotein isolated from presynaptic vesicles of bovine neurones and is found in all neurones, the adrenal medulla, and in various neuroendocrine tumours including islet cell adenomas.[10 11] von Willebrand factor/VIII complex and CD34 are present only on endothelial cells. α Actin is found within all smooth muscle cells.[12 13]

Results

All 24 myxomas showed the typical histological features of clumps and cords of stellate cells with eosinophilic cytoplasm embedded in an abundant myxoid stroma (fig 1A). These cells designated as lepidic (like a butterfly wing scale—one of the more fanciful of pathologists' analogies) also occurred in larger masses arranged as a loose mantle around a space (fig 1B). Immunohistochemical techniques allow recognition of the spatial organisation of the different cell types in myxomas. Endothelial cells identified as containing both CD34 and von Willebrand factor were confined to the centres of clumps of cells and often but not inevitably surrounded a space (fig 2A). The external surface of the myxomas was only partially covered by endothelial cells. Cells staining with PGP 9·5, NSE, S100, and synaptophysin were not present in all myxomas, but when present were confined to the outermost cells of the mantle areas and the isolated stromal cells (fig 2A and B). Eighteen of the 24 myxomas were PGP 9·5 positive, 16 were S100 positive, and 12 were NSE positive. All the myxomas which were NSE positive were also S100 and PGP 9·5 positive. Seven of the 12 NSE positive tumours were synaptophysin positive. In cases with PGP 9·5 positive cells parts of the surface of the myxoma were covered by PGP 9·5 positive cells rather than endothelial cells. Three of the atrial myxomas were derived from patients known to have the familial myxoma syndrome: the stromal cells in one were strongly positive for PGP 9·5 and NSE whereas in the other two they were negative. Smooth muscle cells containing α actin were found predominantly in the base of myxomas where thick walled blood vessels entered from the endocardium. Solid masses of proliferating smooth muscle not obviously related to blood vessels were also present. All of the myxomas showed large numbers of mast cells and plasma cells within the stroma. Macrophages containing haemosiderin were also present in large numbers, reflecting the frequency of haemorrhage from thin walled vessels within the tumour. The stroma showed a biphasic staining pattern with routine haematoxylin and eosin histology stains. There was marked basophilia of the stroma adjacent to clumps of cells while the deeper areas were eosinophilic. The latter areas contained large amounts of insuded fibrinogen, fibronectin, complement, and globulins of plasma origin bound to the connective tissue mucins.

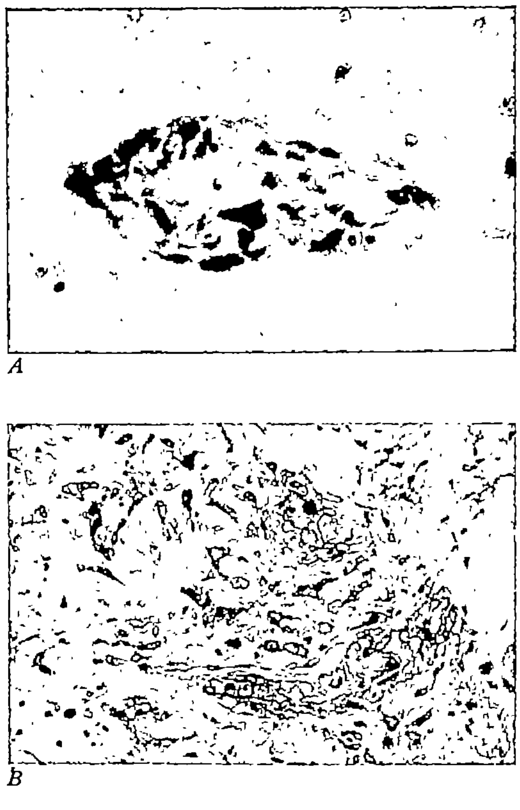

Figure 2 Endothelial cells stained red are positive for von Willebrand factor. (A) The surrounding mantle of myxoma cells are stained deep brown indicating the presence of PGP 9·5. (B) Many isolated myxoma cells within the stroma are positive (brown) for neurone specific enolase. There is also some clustering of positive myxoma cells around endothelial cells (stained red) although no vascular lumen is apparent.

Discussion

The identification of tumour origins by specific antigen expression has to be approached with caution.[14] The phenotypic expression in tumours is variable and does not necessarily reflect their origin. Endocrine functions and expression of neuroendocrine markers that seem inappropriate and independent of the morphological phenotype of the tumour are widely reported in the bowel, ovary, and liver.[15] Nevertheless tumours in which these very aberrant expressions are found are usually malignant whereas myxomas are not. There is also no perfect marker of neuroendocrine differentiation and following the development and use of any particular antibody, its limitations often becomes apparent. For example the gamma subunit of NSE is often expressed in tumours clearly not of neural origin.[16] PGP 9·5 is present in a small proportion of atrial myocytes, in the renal tubule,[17] and in some smooth muscle cells. S100 is also found in adipose cells. Nevertheless, the concordance of positive marking of myxoma stromal cells with three widely used different neuroendocrine markers is presumptive evidence of a neuroendorine differentiation pattern. Expression of tumour antigens is always capricious and the fact that some myxomas are totally negative does not necessarily contradict the conclusion.

Neurofibromas of other tissues such as the skin and subcutaneous soft tissue are histologically very complex, containing Schwann cells, perineural cells, fibroblasts, endothelial cells, and occasional axons together with large amounts of connective tissue rich in mucins and containing pericellular type IV collagen.[18] Mast cell infiltration is a regular feature and release of vasoactive amines may contribute to an increase in vascular permeability flooding the stroma with plasma derived proteins. Mast cells are also a source of growth factors acting on the Schwann cell element.[19] All of these morphological features including a plasma rich myxoid stroma, a heterogeneous cell population, and mast cell infiltration are found in atrial myxomas. Morphological similarity between two tumour types cannot prove a similar origin but again is evidence consistent with myxomas being neuroectodermal in origin. The atrial endocardium contains many sensory nerves that are a potential origin for nerve tumours.

Given the rather heterogeneous cell population within atrial myxomas it is hardly surprising that previous studies of histogenesis by electron microscopy have been inconclusive. Two studies suggested that several types of mature mesenchymal cell were present[20,21] while another study regarded the cells as all being of a common undifferentiated mesenchymal form.[22]

Previous immunohistochemical studies did not take sufficient account of the microanatomy of the tumour. A briefly held view (when factor VIII/VWF antigen was shown[23]) that myxomas were of endothelial origin was discounted when it was realised that only cells in the centre of clumps were positive and the myxoma cells were negative.[24,25] Smooth muscle cells are also confined to areas with obvious vascular structures.[26]

The present study suggests that the myxoma surface is partly covered by myxoma cells and partly by endothelium. This observation confirms a previous study of the surface of atrial myxomas by scanning microscopy.[27]

If indeed atrial myxomas are of neural origin the finding makes little difference to clinical practice but may explain some of the rarer associations with other manifestations such as cutaneous lentiginosis. Systemic manifestations of myxomas such as fever, hypergammaglobulinaemia, and weight loss may be related to cytokines released from macrophages or mast cells within the myxoma stroma or release of peptides from the myxoma cells themselves.

1 DeWald G, Dahl R, Spurbveck J, Carney J, Gordon H. Chromosomally abnormal clones and nonrandom telomeric translocations in cardiac myxomas. *Mayo Clin Proc* 1987;62:558–67.
2 Wold L, Lie J. Cardiac myxomas. A clinicopathologic profile. *Am J Pathol* 1980;101:219–34.
3 Harrison L, Said S, Ezekowitz M, Krous H. Vasoactive intestinal polypeptide in cardiac myxoma. *J Thorac Cardiovasc Surg* 1985;79:341–7.
4 Vidaillet HJ Jr, Seward JB, Fyke FE III, Su WPD, Tajik AJ. "Syndrome myxoma": a subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms. *Br Heart J* 1987; 57:247–55.
5 Cordell J, Falini B, Erber W. Immunoenzymatic labelling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal antialkaline phosphatase (APAAP complexes). *J Histochem Cytochem* 1984;32:219–29.
6 Rode J, Dhillon A, Doran J, Jackson P, Thompson R. PGP 9.5 a new marker for human neuroendocrine tumours. *Histopathology* 1985;9:147–58.
7 Schmechel D, Marangos PJ, Brightman M. Neurone-specific enolase is a molecular marker for peripheral and central neuroendocrine cells. *Nature* 1978;276:834–6.
8 Dhillon A, Rode J, Leatham A. Neurone specific enolase: an aid to the diagnosis of melanoma and neuroblastoma. *Histopathology* 1982;6:81–92.
9 Kahn H, Marks A, Thoma H, Baumal R. Role of antibody to S-100 protein in diagnostic pathology. *Am J Clin Pathol* 1983;79:341–7.
10 Gould V, Lee I, Wiedenmann B, Moll R, Chejec G, Franke W. A novel marker for neurons, certain neuroendocrine cells, and their neoplasms. *Hum Pathol* 1986;17:979–83.
11 Chejfec G, Falkmer S, Grimelius L, *et al*. Synaptophysin. A new marker for pancreatic neuroendocrine tumours. *Am J Surg Pathol* 1987;11:241–7.
12 Sehested M, Hon-Jensen K. Factor VIII related antigen as an endothelial cell marker in benign and malignant disease. *Virchows Archiv [A]* 1981;391:217–25.
13 Skalli O, Ropraz P, Trzeciak A, Benzonana G, Gillessen D, Gabbiani G. A monoclonal antibody against alph-smooth muscle actin: a new probe for smooth muscle differentiation. *J Cell Biol* 1986;103:2787–96.
14 Gould V. Histogenesis and differentiation: a re-evaluation of these concepts as criteria for the classification of tumour. *Hum Pathol* 1986;17:212–4.
15 Wang J, Dhillon A, Sankey E, Wightman A, Lewin J, Scheuer P. Neuroendocrine differentiation in primary neoplasms of the liver. *J Pathol* 1991;163:61–67.
16 Schmechel DE. y subunit of the glycolytic enzyme enolase: nonspecific or neuron-specific? *Lab Invest* 1985;52:239–42.
17 Wilson P, Barber P, Hamid Q, *et al*. The immunolocalization of protein gene product 9·5 using rabbit polyclonal and mouse monoclonal antibodies. *Br J Exp Pathol* 1988; 69:91–104.
18 Peltonen J, Jaakkola S, Lebwohl M, *et al*. Cellular differentiation and expression of matrix genes in Type 1 neurofibromatosis. *Lab Invest* 1988;59:760–71.
19 Riccardi V. Mast-cell stabilization to decrease neurofibroma growth. Preliminary experience with Ketotifen. *Arch Dermatol* 1987;123:1011–6.
20 Stein A, Mauro J, Thibodeau L, Alley R. The histogenesis of cardiac myxomas: relation to other proliferative diseases of subendothelial vasoformative reserve cells. *Pathol Annu* 1969;4:293–312.
21 Ferrans V, Roberts W. Structural features of cardiac myxomas: histology, histochemistry and electron microscopy. *Hum Pathol* 1973;4:111–46.
22 Feldman P, Horvarth E, Kovacs K. An ultrastructural study of seven cardiac myxomas. *Cancer* 1977;40:2216–32.
23 Morales A, Fine G, Castro A, Nadgi M. Cardiac myxomas (endocardioma): an immunohistochemical assessment of histogenesis. *Hum Pathol* 1981;12:896–9.
24 Boxer M. Cardiac myxoma: an immunoperoxidase study of histogenesis. *Histopathology* 1984;8:861–72.
25 McComb R. Heterogeneous expression of factor VIII/von Willebrand factor by cardiac myxoma cells. *Am J Surg Pathol* 1984;8:539–44.
26 Landon G, Ordonez N, Guarda L. Atrial myxomas: an immunohistochemical study using endothelial, histiocytic, and smooth-muscle cell markers. *Arch Pathol Lab Med* 1986;110:116–20.
27 Zhang P-F, Jones J, Anderson W. Cardiac myxomas correlative study by light, transmission, and scanning electron microscopy. *Am J Cardiovasc Pathol* 1989;2: 295–300.

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Myocardial dysfunction in treated adult hypopituitarism: a possible explanation for increased cardiovascular mortality

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Abstract

***Objective*—To assess cardiac structure and function in patients with treated hypopituitarism and to determine their relation to the degree of growth hormone deficiency and body composition pattern.**

***Design*—26 patients with treated hypopituitarism were studied by cross sectional and Doppler echocardiography and by exercise testing. The results were analysed and their relation to the degree of growth hormone deficiency and body composition determined.**

***Setting*—All tests were performed in the department of cardiology and the unit of metabolic medicine at a tertiary referral centre.**

***Patients*—Patients with hypopituitarism referred for endocrine assessment.**

***Main outcome measures*—Left ventricular mass, left ventricular diastolic function, and exercise capacity in patients with hypopituitarism and their relation to growth hormone deficiency.**

***Results*—Mean (SD) serum concentration of insulin-like growth factor 1 (IGE-1), a measure of growth hormone deficiency, was 82·4 (45) μg/l. Lean body mass calculated by measuring total body potassium was 50 (9) kg. All patients had a normal left ventricular mass index and a normal left ventricular ejection fraction. Eight patients had abnormal left ventricular diastolic function. There was a significant correlation between IGF-1 and left ventricular mass ($r = 0\cdot45$, $p < 0\cdot02$). Lean body mass was also significantly correlated with left ventricular mass ($r = 0\cdot78$, $p < 0\cdot0001$) and left ventricular diastolic function ($r = -0\cdot63$, $p < 0\cdot01$). The mean exercise duration was 8·6 (3·6) minutes. There was a significant correlation between serum IGF-1 and the rate-pressure product on exercise ($r = 0\cdot47$, $p < 0\cdot01$). Seven patients had planar ST segment depression $> 0\cdot1$ mV during exercise testing. In five of these patients there was rapid resolution of ST segment depression immediately after exercise. Two patients developed considerable ST segment depression, and subsequent coronary angiography showed normal coronary arteries. Exercise-induced ST segment depression was not related to the severity or duration of growth hormone deficiency or serum cholesterol concentration.**

***Conclusions*—This study suggests that left ventricular mass and the rate-pressure product are related to the degree of growth hormone deficiency, that left ventricular diastolic dysfunction is frequently seen in hypopituitarism, and that these patients may have ischaemic-like ST segment changes during exercise testing. These findings may explain the increased cardiovascular mortality in patients with hypopituitarism and may also have implications for growth hormone replacement therapy in adults.**

Patients who develop hypopituitarism in adulthood have conventionally received replacement therapy with thyroxine, cortisone, and sex hormones but not growth hormone. This has in part been because of the limited availability of growth hormone and the belief that growth hormone has no important action once final linear growth has been achieved.[1] However, growth hormone has now been made available in essentially unlimited amounts and in a pure synthetic form by genetic engineering techniques. Also, recent evidence has suggested that the increased cardiovascular mortality, in particular a high incidence of myocardial infarction and heart failure, seen in patients with treated hypopituitarism may be due to growth hormone deficiency.[2]

Growth hormone is known to be a potent agent affecting anabolism and lipolysis. Adults with growth hormone deficiency are known to have an altered body composition with excess body fat and decreased lean body mass.[3] This form of change in body composition has been previously shown to be associated with an increased risk of cardiovascular disease in symptom free individuals.[4 5] In addition, growth hormone seems to be important in the regulation of plasma lipids, with deficiency of growth hormone often causing hypercholesterolaemia.[6 7]

The aim of the present study was to assess cardiac structure and function in patients with treated hypopituitarism and to determine their relation to the degree of growth hormone deficiency and body composition pattern.

Patients and methods

PATIENTS

Patients recruited into the study had documented hypopituitarism mostly resulting from pituitary or parapituitary tumours treated surgically, with radiotherapy, or with both. All had been on hormonal replacement therapy with thyroxine and adrenal and sex steroids, if appropriate, for at least one year. Optimal substitution with thyroxine and adrenal steroids were defined as a total serum thyroxine (T4) within the normal reference range and at least one plasma cortisol value > 350 nmol/l during the day. In addition, all patients were severely deficient in growth hormone, defined as a growth hormone response of < 5 mU/l during an insulin induced hypoglycaemia test (serum glucose $< 2{\cdot}2$ mmol/l) or, if hypoglycaemia was contraindicated, a growth hormone response of < 5 mU/l in response to 50 μg oral clonidine. No patient had previously received growth hormone replacement.

METABOLIC ASSESSMENT

Lean body mass was calculated from total body potassium[8] which was measured in a whole-body potassium-40 counter (MRC Cyclotron Unit, Hammersmith Hospital). Serum insulin-like growth hormone factor (IGF-1), a measure of growth hormone deficiency, was measured by radioimmunoassay.[9] The mean value of IGF-1 in our laboratory in 40 healthy volunteers was 215 (40) μg/l.

ECHOCARDIOGRAPHY

Each patient was examined in the left lateral supine position by cross sectional and Doppler echocardiography with a phased array sector scanner (General Electric Pass 11, 3·5 MHz transducer) in a standardised examination protocol.[10] Left ventricular septal and posterior wall thickness, and cavity dimensions were measured from the parasternal left ventricular short axis projections at the chordae and papillary muscle junction by cross sectionally guided M mode echocardiography. Left ventricular mass was determined by an area × length method which has been previously been validated in humans[11] with all measurements taken at end diastole and at end expiration. Two echocardiographic views are required to make this calculation: a parasternal short axis view of the left ventricle at the papillary muscle tip level to determine the area of the myocardium and an apical four chamber view that maximises the distance from the mitral valve annulus to the left ventricular apex to determine the length of the ventricle (fig 1). The following formula was used to calculate left ventricular mass: $\text{LV mass} = 1{\cdot}04\,(5/6\,A_1 x l_1 - 5/6\,A_2 x l_2)$ where A_1 and A_2 represent the epicardial and endocardial areas respectively (measured by planimetry) and l_1 and l_2 represent the length of the left ventricle from mital annulus to epicardial and endocardial borders respectively. Left ventricular mass index was determined by dividing the left ventricular mass by the patient's body surface area ($S = M^{0{\cdot}425} \times H^{0{\cdot}725} \times 71{\cdot}84$, where S = body surface area (cm^2), M = body mass (kg), and H = height (cm)).

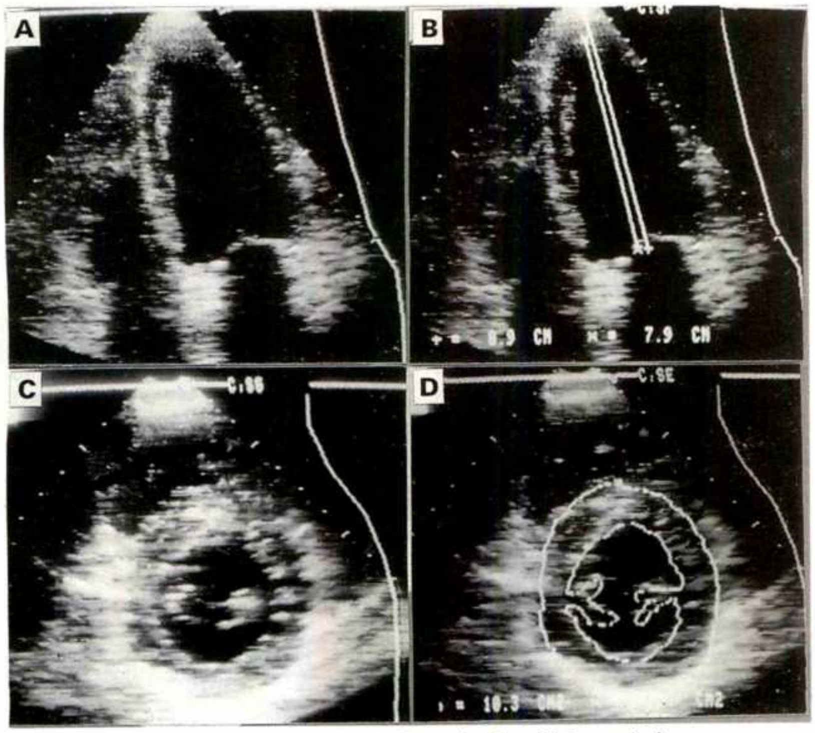

Figure 1 Cross sectional technique for the determination of left ventricular mass. (A) Apical four chamber view, (B) length of left ventricle from mitral annulus to epicardial and endocardial borders, (C) parasternal short axis view, (D) epicardial and endocardial areas measured by planimetry. See text for method of calculation.

DOPPLER STUDIES

Pulsed Doppler examination of transmitral flow was recorded from the apical four chamber view with reference to the cross sectional echocardiographic image. The sample volume was positioned between the mitral annulus and the tips of the mitral leaflets with the position adjusted to maintain the sample volume at an angle as near parallel to transmitral flow as possible by using the audible signal and spectral velocity display. When the maximum transmitral velocity for the early filling wave was detected, we recorded the velocity profile at 50 mm/s with the patient in passive end expiration. The peak flow velocities of the early and atrial waves were measured from the three consecutive cardiac cycles that showed the highest measurable velocity profiles.

The isovolumic relaxation time (IVRT) was measured from the apical five chamber view by placing the continuous wave Doppler beam between the mitral and aortic valve junction. The interval between the end of the aortic velocity envelope and the onset of the early filling wave was taken to represent the isovolumic relaxation time. Abnormal left ventricular diastolic function was defined as follows: IVRT > 82 ms and E/A ratio $< 1{\cdot}5$ between the ages of 20 and 29; IVRT > 92 ms and E/A ratio $< 1{\cdot}4$ between the ages of 30 and 49; IVRT > 100 ms and E/A ratio $< 0{\cdot}8$ between the ages of 50 and 59.[12 13]

EXERCISE ASSESSMENT

Symptom-limited, graded multistage treadmill exercise testing according to Bruce's standard protocol[14] was performed by all patients in a temperature and humidity controlled environment with standard safety precautions. Heart rate and blood pressure were measured at the end of each stage of the protocol and exercise was stopped by symptoms such as leg weakness, shortness of breath, or exhaustion. Data

Table 1 Patient details

Patient	*Sex*	*Age (yr)*	*BMI (kg/m^2)*	*DOH (yr)*	*Cholesterol (mmol/l)*	*Triglyceride (mmol/l)*	*Diagnosis*	*Replacement* therapy*
1	M	34	26·6	15	8·67	2·0	Cushing's	A, B, C
2	M	59	26·2	28	7·78	3·1	CP	A, B, C, D
3	M	47	28·2	5	9·02	3·4	CP	A, B, C, D
4	M	64	25·0	9	6·09	1·2	Prolactinoma	A, B, C
5	M	59	25·7	9	7·94	1·3	Prolactinoma	A, C
6	M	52	26·0	3	5·92	3·9	Cushing's	A, B
7	M	27	19·4	6	7·41	1·2	Pinealoma	A, B, C
8	M	45	29·9	3	6·09	1·7	NFA	A, B, C
9	M	59	29·5	20	5·37	0·9	NFA	A, B, C
10	M	50	33·8	6	3·35	1·0	Prolactinoma	B, C
11	M	44	32·4	4	8·64	1·1	NFA	A
12	M	41	33·5	2	4·93	1·1	Prolactinoma	C
13	M	63	33·9	1	9·37	1·2	NFA	A, B, C
14	F	53	25·1	21	10·0	1·9	CP	A, B, D
15	F	59	27·5	15	10·0	1·9	NFA	A, B, E
16	F	57	29·7	1	5·72	0·6	NFA	A, B
17	F	47	29·1	16	7·63	1·7	Cushing's	A, B
18	F	26	21·8	3	7·79	1·4	CP	A, B, D, E
19	F	38	30·5	3	6·90	1·0	Cushing's	A, E
20	F	41	32·1	6	4·67	1·3	Prolactinoma	A, B, D
21	F	44	31·1	3	9·00	9·2	Prolactinoma	A, B, D, E
22	F	53	26·3	6	5·60	1·1	Meningioma	A, B
23	F	49	23·5	4	7·60	1·9	NFA	A, B, D
24	F	43	32·7	3	6·28	1·8	Prolactinoma	D
25	F	27	26·5	4	5·20	1·3	CP	D
26	F	41	19·9	3	6·64	0·7	NFA	B

BMI, body mass index; DOH, duration of hypopituitarism; CP, craniopharyngeoma; NFA, non-functioning adenoma.
*A, thyroxine; B, adrenal steroids; C, testosterone; D, desmopressin; E, oestrogen/progesterone.

from the exercise tests were analysed by computer assisted methods to give exercise time, workload, heart rate × systolic blood pressure product at peak exercise, and extent of electrocardiographic ST segment change. The level of the ST segment 0·08 s after the J point was measured in each lead using an average beat every one minute and only planar ST segment depression $> 0·1$ mV was considered to be abnormal. ST segment depression found by the average beat analysis was confirmed on the actual electrocardiogram by manual measurement.

Results

PATIENT CHARACTERISTICS

Twenty six patients (13 men and 13 women) with confirmed hypopituitarism were recruited into the study during the period December 1989–January 1991. All patients attended the endocrinology clinic in our hospital. The mean (SD) age was 46 (11) years (range 26–64 years). Table 1 shows the primary diagnosis, duration of hypopituitarism, duration of hormone replacement therapy, and other patient details. The lean body mass and body fat were 50 (9) kg (range 38–64 kg) and 30 (11) kg (range 11–55 kg) respectively. The degree of growth hormone deficiency, assessed by serum concentration of insulin-like growth factor (IGF-1) was 82 (45) μg/l (range 21–221 μg/l). There was a significant positive correlation between IGF-1 and lean body mass in our patients ($r = 0·5$; $p < 0·01$). No patient had a previous history of ischaemic heart disease, peripheral vascular disease, or hypertension except for one patient with Cushing's disease (patient 6) whose blood pressure had been raised before his pituitary tumour was removed but then returned to normal after the operation.

ECHOCARDIOGRAPHIC AND DOPPLER CHARACTERISTICS

All patients had a normal left ventricular ejection fraction (67 (8)%) and a normal left ventricular mass index (men 101 (17) g/m^2 range 76–132 g/m^2; women 84 (20) g/m^2 range 56–119 g/m^2) but the distribution was skewed towards the lower end of the normal range (skew 0·25). Patients who had Cushing's disease did not have higher left ventricular mass indexes. Table 2 shows the other echocardiographic and Doppler characteristics. Compared with the age related reference values established by previous investigators,[13 14] thirteen patients (50%) had an abnormally prolonged isovolumic relaxation time (112 (15) ms) and eight (31%) had both an increased isovolumic relaxation time (103 (8) ms) and evidence of abnormal left ventricular filling (E/A ratio 1·06 (0·25) table 3). There was significant correlation between left ventricular mass and serum IGF-1 ($r = 0·45$; $p < 0·02$). Left ventricular mass and left ventricular filling were related to lean body mass ($r = 0·78$ $p < 0·0001$; $r = -0·63$ $p < 0·001$) (figure 2A–C). There was no relation between left ventricular mass and duration of hypopituitarism.

EXERCISE ASSESSMENTS

The mean exercise duration during the Bruce protocol was 8·6 (3·6) minutes. The exercise test was terminated because of leg weakness in seven patients, by shortness of breath in eight

Table 2 Echocardiographic and Doppler characteristics of study patients

Variable	*Mean (SD)*	*Range*
LV septum (cms)	0·85 (0·2)	0·5–1·1
LV posterior wall (cms)	0·84 (0·2)	0·6–1·1
LV internal diameter (cms)	4·82 (0·4)	4·1–5·6
LV mass (male) (g)	212 (49)	138–323
LV mass (female) (g)	148 (42)	92–231
IVRT (ms)	103 (16)	72–140
E (cm/s)	64 (13)	38–87
A (cm/s)	55 (10)	36–71
E/A ratio	1·18 (0·31)	0·74–1·94

LV, left ventricle; IVRT, isovolumic relaxation time; E, early filling velocity; A, atrial filling velocity.

Table 3 Details of patients with abnormal left ventricular diastolic function

Patient	*Age (yr)*	*Heart rate*	*IVRT (ms)*	*E (cm/s)*	*A (cm/s)*	*E/A*	*Max ST depression on exercise (mV)*
1	34	70	108	66	48	1·37	None
3	47	65	96	66	58	1·15	0·22
7	27	77	92	78	62	1·26	0·13
8	45	69	111	49	62	0·8	0·19
9	59	78	108	39	51	0·77	None
11	44	63	94	72	61	1·17	None
12	41	74	112	48	65	0·74	None
18	26	73	104	75	59	1·25	None

IVRT, isovolumic relaxation time; E, early filling velocity; A, atrial filling velocity.

patients, and by exhaustion in 11 patients. No patient developed chest pain during exercise. A significant correlation was seen between serum IGF-1 and the rate-pressure product (systolic blood pressure × heart rate) at peak exercise ($r = 0·47$; $p < 0·01$; fig 2D) but not with exercise duration ($r = 0·1$; $p = NS$). Baseline electrocardiograms were normal in all patients except for patients 8 and 15 who had minor ST segment abnormalities in the lateral chest leads. Seven patients developed planar ST segment depression $> 0·1$ mV during exercise testing (maximum ST segment depression in these seven patients was 0·18 (0·03) mV). In five of these patients the ST segment depression occurred at a high workload with immediate resolution after exercise. Two patients developed ST segment depression after a few minutes of exercise with slow resolution during the post-exercise period. Subsequent coronary angiography showed no abnormality of the epicardial coronary arteries. Exercise-induced ST segment depression was not related to the severity or duration of growth hormone deficiency or to serum cholesterol concentration. Three of these seven patients also had abnormal left ventricular diastolic function.

Discussion

The principal findings of this study were firstly that in patients with treated hypopituitarism but without growth hormone replacement therapy the left ventricular mass and maximum cardiac work achieved on exercise were inversely related to the degree of growth hormone deficiency. Second, left ventricular diastolic dysfunction seems to be a frequent finding in these patients and furthermore these patients often have ischaemia-like ST segment changes during exercise testing.

All of the patients in this study had a normal left ventricular mass index with a trend towards the lower end of the normal range. The relation between left ventricular mass and body weight/lean body weight seen in this study is similar to that reported in healthy individuals.[15] However, the relation between left ventricular mass and the degree of growth hormone deficiency is surprising, because it suggests that growth hormone may still be necessary for the maintenenace of cardiac size in adulthood. Growth hormone administration in adult rats increased left ventricular mass in proportion to the observed increase in body weight.[16] In humans, however, four months of growth hormone replacement therapy given to growth hormone deficient adults had no significant effect on left ventricular mass.[17] It is possible, however, that left ventricular mass may increase with longer term replacement therapy. Whether our measurements of left ventricular mass are indeed "normal" for these patients is open to debate; however, the inverse relation between the degree of growth hormone deficiency and peak cardiac work on exercise (rate-pressure product) suggests that the exercise capacity of the heart is impaired in hypopituitarism. Nonetheless, the mechanism for exercise

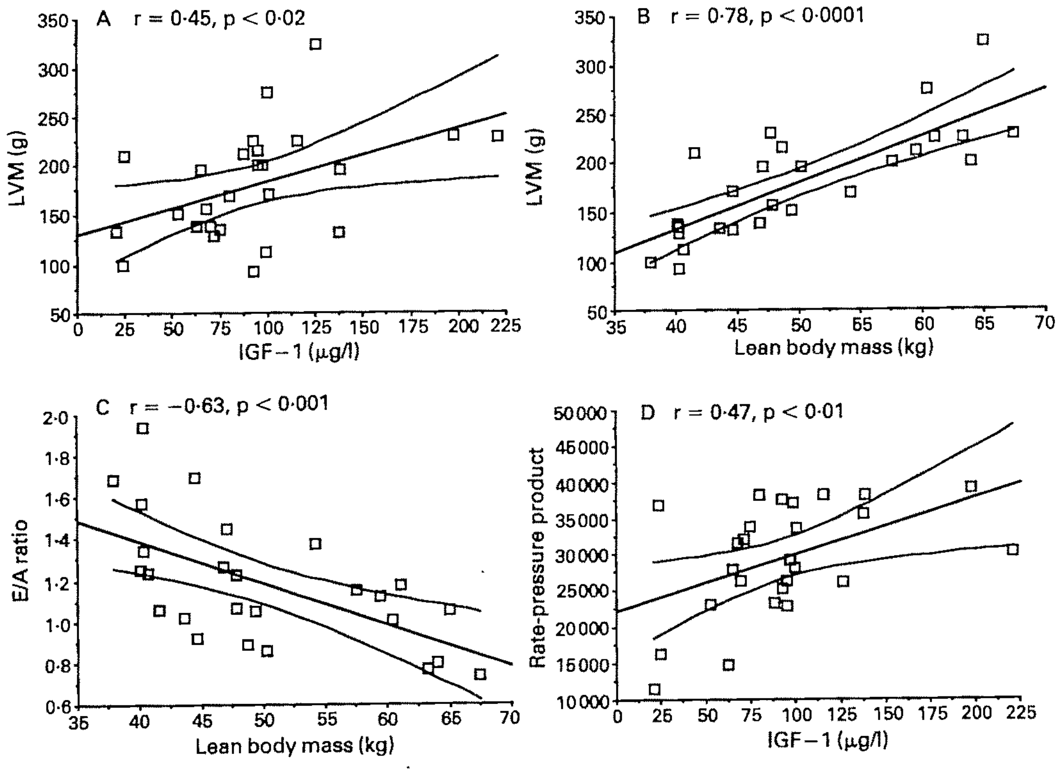

Figure 2 (A) Relation between serum IGF-1 and left ventricular mass (LVM), (B) relation between lean body mass and LVM, (C) relation between lean body mass and left ventricular filling (E/A ratio), (D) relation between serum IGF-1 and the rate-pressure product. The regression line and its 95% confidence limits are shown for each scattergram.

limitation in this patient population is complex and probably relates to a combination of peripheral muscle atrophy, deconditioning, and changes in cardiac function. In the present study, only seven of the 26 patients had their exercise test stopped because of leg weakness while the rest were stopped by shortness of breath or extreme exhaustion.

The frequent finding that abnormalities of left ventricular diastolic function in the presence of normal left ventricular systolic function in patients with hypopituitarism has not been described before. It has been suggested that these abnormalities are a possible precursor of left ventricular systolic failure and may be the earliest manifestations of cardiac failure.[18] These abnormalities may explain the increased incidence of heart failure in patients with hypopituitarism.[2] Whether growth hormone replacement therapy will improve this abnormality is not known. However, in healthy people growth hormone therapy increased myocardial contractility and cardiac output[19] and therefore it might be able to reverse the diastolic abnormalities observed in this study. Growth hormone therapy was shown to benefit one growth hormone deficient patient with severe cardiac failure.[20]

Nor has the increased incidence of ST segment depression on exercise, similar to that seen in patients with coronary artery disease, been reported before in patients with hypopituitarism. Most of these patients developed these abnormalities at a high workload; however, two patients did have ST segment depression at a low workload and subsequent coronary angiography was normal. Although these may have been false positive electrocardiographic responses to exercise testing, it may in light of the known increased cardiovascular mortality in these patients suggest that they have small coronary vessel disease or some undisclosed form of myocardial disease. McHenry and colleagues reported that symptom free patients who had not had coronary angiography had about a 40% chance of developing coronary artery disease over a 14 year period if they had an ischaemic-type response to exercise.[21] If the outcome were similar in our patients, with their additional risk of increased serum cholesterol, this could explain the increased incidence of myocardial infarction observed in patients with treated hypopituitarism.[2]

We cannot be certain that inadequate replacement therapy of other pituitary dependent hormones—for example, thyroxine, cortisol, and oestrogen therapy, was not the reason for the abnormal cardiac findings in our patients. However, all our patients had been euthyroid for at least one year and had thyroxine (T_4) concentrations within the normal range. Patients with Cushing's disease had been cured for at least three years and sex hormones were prescribed to all patients. In addition no patients had hypertension or diabetes mellitus.

Though we did not study age matched controls our criteria for abnormality were strictly defined and lay outside the 95% confidence intervals of the normal range reported by others.

In conclusion, we found that patients with treated hypopituitarism had abnormalities of cardiac structure and function that may explain the increased incidence of cardiovascular mortality observed in these patients. The relation with the degree of growth hormone deficiency may have implications for growth hormone replacement therapy in adults.

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1 Besser GM. Anterior pituitary. In: Hall R, Besser GM, eds. *Fundamental of clinical endocrinology*. London: Churchill Livingstone, 1989:1–30.

2 Rosen T, Bengtsson B. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990;336:285–8.

3 Saloman F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* 1989;321:1797–803.

4 Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow-up of participants in the study of men born in 1913. *BMJ* 1984;288:1401–4.

5 Lapidus L, Bengtsson C, Larrson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow-up of participants in the population study of women in Gothenberg, Sweden. *BMJ* 1984;289:1257–61.

6 Merimee T, Hollander W, Fineberg E. Studies of hyperlipidaemia in the hGH-deficient state. *Metabolism* 1972;21:1053–61.

7 Blackett PR, Weech PK, McConathy WJ, Fesmire JD. Growth hormone in the regulation of hyperlipidaemia. *Metabolism* 1982;31:117–20.

8 Boddy K, King PC, Hume R, Weyers E. The relationship of total body potassium to height, weight and age in normal adults. *J Clin Pathol* 1972;25:512–7.

9 Teale JD, Marks V. The measurement of insulin-like growth factor 1: clinical applications and significance. *Ann Clin Biochem* 1986;23:413–24.

10 Foale R, Nihoyannopoulos P, McKenna W, *et al*. Echocardiographic measurement of the normal adult right ventricle. *Br Heart J* 1986;56:33–44.

11 Helak JW, Reichekk N. Quantitation of human left ventricular mass and volume by two-dimensional echocardiography: in vitro validation. *Circulation* 1981;63:1398–407.

12 Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;59:672–9.

13 Gardin JM, Rohan MK, Davidson, *et al*. Doppler transmitral flow velocity parameters: relationship between age, body surface area, blood pressure and gender in normal subjects. *Am J Noninvas Cardiol* 1987;1:3–10.

14 Bruce RA, Blackmon JR, Jones JW, Strait G. Exercise testing in adult normal subjects and cardiac patients. *Pediatrics* 1963;32:742–56.

15 Devereux RB, Lutas EM, Casale PN, *et al*. Standardisation of M mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 1984;4:1222–30.

16 Lei LQ, Rubin SA, Fishbein MC, Cardiac architectural changes with hypertrophy induced by excess growth hormone in rats. *Lab Invest* 1988;59:357–62.

17 Jorgensen JOL, Pedersen SA, Thuesen L, *et al*. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1989;i:1221–5.

18 Dougherty AH, Naccerelli GV, Gray EL, Hicks CH, Golstein RA. Congestive heart failure with normal systolic function. *Am J Cardiol* 1987;54:778–82.

19 Thuesen L, Christiansen JS, Sorensen KE, Jorgensen JOL, Orskov H, Henningsen P. Increased myocardial contractility following growth hormone administration in normal man: an echocardiographic study. *Dan Med Bull* 1988;35:193–6.

20 Cuneo RC, Wilmhurst P, Lowy C, McGauley G, Sonksen PH. Cardiac failure responding to growth hormone. *Lancet* 1989;i:838–9.

21 McHenry PL, O'Donnell J, Morris SN, Jordan JJ. The abnormal exercise electrocardiogram in apparently healthy men: a predictor of angina pectoris as an initial coronary event during long-term follow-up. *Circulation* 1984;70:547–52.

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CASE REPORT

Recurrent ventricular arrhythmias complicating myocardial infarction in the presence of phaeochromocytoma

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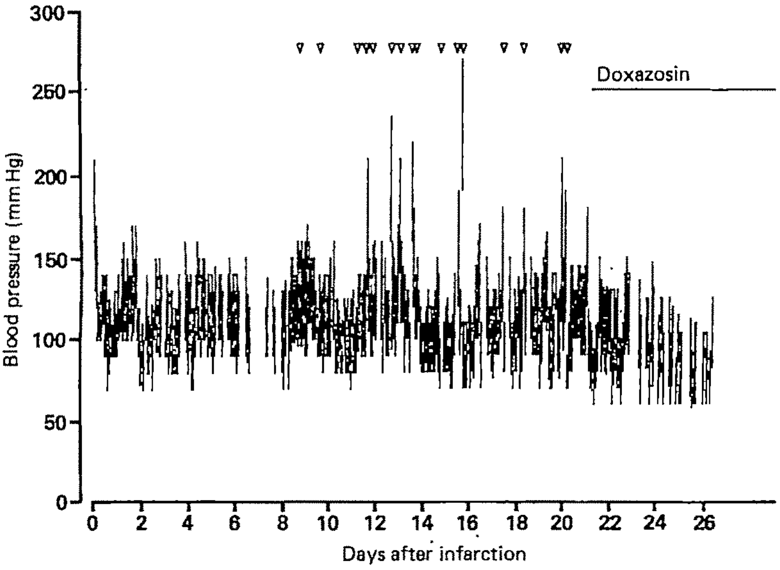
Abstract

After an acute myocardial infarction a 49 year old man developed late recurrent severe ventricular arrhythmias coincident with transient hypertensive episodes. A phaeochromocytoma was diagnosed on the basis of the urinary concentration of catecholamines and computerised tomography of the adrenal glands. After stabilisation of his cardiac rhythm and blood pressure with α and β adrenergic blockade and antiarrhythmic treatment the right adrenal gland, which contained the tumour, was successfully resected.

The diagnosis of a phaeochromocytoma should be considered when recurrent ventricular arrhythmias are associated with intermittent hypertension after myocardial infarction.

A phaeochromocytoma is an uncommon tumour that it is important to diagnose because of the risk of hypertensive crises and malignancy.[1-3] The most common symptoms are headache, palpitation, and sweating; and the combination of this triad with hypertension should raise the suspicion of a phaeochromocytoma.[1,4,5] The diversity of presentation, however, often delays the diagnosis,[2] often with fatal results. We report a patient with an unusual presentation of this tumour.



Blood pressure recordings during the first 26 days after infarction showing the relation between episodes of ventricular fibrillation (∇) and fluctuations in blood pressure and the response to doxazosin.

Case report

A 49 year old man with no previous cardiac history was admitted by the mobile coronary care unit with an acute myocardial infarction. He had a one year history of hypertension and smoked 30 cigarettes a day. Thrombolytic therapy was not given because the initial blood pressure (210/130 mm Hg) was so high. After pain relief by intravenous diamorphine he was treated routinely with oral propranolol (10 mg four times a day) and subcutaneous heparin (10 000 units twice a day). His blood pressure settled to 124/100 mm Hg within two hours. The peak activity of serum creatine kinase was 2178 IU/l (normal <180) (MB isoenzyme 297 IU/l (normal <25)).

Thirty six hours after admission the blood pressure rose again to around 170/100 mm Hg and he developed atrial fibrillation with a fast ventricular response and short bursts of broad complex trachycardia. He reverted to sinus rhythm after treatment with digoxin. Four hours later he had bursts of ventricular tachycardia that recurred despite treatment with intravenous lignocaine and flecainide but settled after intravenous mexiletine. He continued to have occasional transient episodes of atrial fibrillation and ventricular extrasystoles with a rather fluctuating blood pressure until 10 days after admission when he collapsed with ventricular fibrillation which was easily corrected by direct current shock. Frequent episodes of ventricular fibrillation and ventricular tachycardia recurred over the subsequent 10 days (figure) despite successive treatment with lignocaine, mexiletine, procainamide, quinidine, amiodarone, and propafenone. Immediately after each episode his blood pressure was usually raised, often considerably, though it was relatively normal when his rhythm was stable. His basic sinus rhythm did not fluctuate unduly; usually it remained between 60 and 80 beats per minute.

Echocardiography showed infarction and aneurysmal dilatation of the left ventricular apex and lower septum. Twenty four hour urinary catecholamine excretion was 2·34 (normal range 0·02–0·97) μ mol, and assay showed increased excretion of noradrenaline (2302 nmol (normal 50–560)), adrenaline (29 nmol (normal 5–120)), and dopamine (639 nmol (normal 300–3900)).

Ultrasonography showed an enlarged right adrenal gland and this was confirmed by computerised tomography which showed a tumour measuring 4 cm by 2 cm in the right adrenal gland.

On day 21 after admission doxazosin (1 mg daily) was introduced and treatment with amiodarone, propafenone, and metoprolol was continued. Within a few hours of the first dose both the heart rhythm and blood pressure became more stable (figure). Ventricular fibrillation did not recur though bursts of multifocal ventricular extrasystoles occasionally occurred and on day 29 there was one further prolonged episode of self-terminating ventricular tachycardia associated with transient hypertension (200/120 mm Hg). When the dose of doxazosin was increased to 3 mg daily good control of rhythm and blood pressure was restored. Thirty two days after admission he was transferred to the Royal Victoria Hospital Belfast for adrenalectomy. Doxazosin was replaced by phenoxybenzamine and his condition remained stable until the right adrenal gland, which contained a phaeochromocytoma, was removed 15 weeks after the initial presentation. Postoperatively he required high doses of noradrenaline, dopamine, and dobutamine and plasma expansion by rapid intravenous fluid infusion to maintain an adequate blood pressure. These were gradually reduced and when he was discharged six weeks after surgery he was normotensive, in sinus rhythm, and without medication.

At review five months after operation he was well apart from postural hypotension, which responded to xamoterol. Ambulatory electrocardiographic monitoring showed frequent benign but symptomatic ventricular extrasystoles that responded to propafenone. Electrophysiological studies showed no inducible arrhythmia. Urinary concentrations of catecholamines were normal.

Discussion

Patients with phaeochromocytoma can have atrial and ventricular arrhythmias associated with electrocardiographic changes that are consistent with acute myocardial ischaemia.[6,7] Fatal myocardial infarction in a young man with undiagnosed phaeochromocytoma has been reported and his sudden death was presumably due to a fatal arrhythmia complicating the infarct.[8] However, we are not aware of any previous case of such severe and persistent ventricular arrhythmias complicating myocardial infarction in the presence of a phaeochromocytoma.

Arrhythmias are so commonly accompanied by a reduction in blood pressure so the curious finding of hypertension with atrial fibrillation on the second day after infarction, and especially immediately after correction of most episodes of ventricular fibrillation, raised the suspicion of intermittent excessive catecholamine release. His life-threatening arrhythmias continued to recur despite treatment with numerous antiarrhythmic agents and β adrenergic blockade and settled only after the addition of doxazosin, an α adrenergic blocking drug, to his treatment regimen. This response accorded with the predominant release of noradrenaline.

Catecholamine induced cardiomyopathy characterised by diffuse focal myocardial necrosis[9,10] may be associated with electrocardiographic abnormalities resembling myocardial infarction[9,11,12] but with normal coronary arteries.[11,12] The clinical presentation in this case of classic chest pain, electrocardiographic changes, and raised serum enzymes in a heavy smoker was typical of coronary thrombosis with infarction. Intermittent excessive noradrenaline release presumably enhanced the arrhythmogenicity of the ischaemic myocardium.

Phaeochromocytoma is rare and can be fatal. This tumour should be suspected in any patient with recurrent arrhythmias associated with hypertension after acute myocardial infarction.

We thank Mr C Russell and Dr B Atkinson for their assistance in the management of this patient.

1 Gifford RW Jr, Kvale WR, Maher FT, Roth GM, Priestley JT. Clinical features, diagnosis and treatment of pheochromocytoma: a review of 76 cases. *Mayo Clin Proc* 1964;39:281–302.
2 Ross EJ, Griffith DNW. The clinical presentation of phaeochromocytoma. *Q J Med* 1989;71:485–96.
3 Sheps SG, Jiang N-S, Klee GG, van Heerden JA. Recent developments in the diagnosis and treatment of pheochromocytoma. *Mayo Clin Proc* 1990;65:88–95.
4 Plouin PF, Degoulet P, Tugaÿe A, Ducrocq M-B, Ménard J. Le dépistage du phéochromocytome: chez quels hypertendus?: etude sémiologique chez 2585 hypertendus dont 11 ayant un phéochromocytome. *Nouv Presse Med* 1981;10:869–72.
5 Bravo EL, Gifford RW Jr. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 1984; 311:1298–303.
6 Haas GJ, Tzagournis M, Boudoulas H. Pheochromocytoma: catecholamine-mediated electrocardiographic changes mimicking ischaemia. *Am Heart J* 1988;116:1363–5.
7 Manning LV, Barratt S. Normotension, ventricular tachycardia and palpitation: an unusual presentation of phaeochromocytoma. *Br J Clin Pract* 1989;43:163–4.
8 Priest WM. Phaeochromocytoma with fatal myocardial infarction in a man aged 22. *BMJ* 1952;ii:860–2.
9 Van Vliét PD, Burchell HB, Titus JL. Focal myocarditis associated with phaeochromocytoma. *N Engl J Med* 1966;274:1102–8.
10 Sardesai SH, Mourant AJ, Sivathandon Y, Farrow R, Gibbons DO. Phaeochromocytoma and catecholamine induced cardiomyopathy presenting as heart failure. *Br Heart J* 1990;63:234–7.
11 McGonigle P, Webb SW, Adgey AAJ. Phaeochromocytoma: an unusual cause of chest pain. *BMJ* 1983;286: 147–8.
12 Shaw TRD, Rafferty P, Tait GW. Transient shock and myocardial impairment caused by phaeochromocytoma crisis. *Br Heart J* 1987;57:194–8.

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PRACTICE REVIEWED

Impact of catheter and surgical ablation on arrhythmia treatment in a tertiary referral centre

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Abstract

Invasive cardiac electrophysiology studies began as diagnostic studies. The past decade has seen the introduction of several new treatments which have broadened the scope of invasive electrophysiology studies. In particular, the development of catheter ablation techniques increasingly allows curative treatment to be delivered in the catheter laboratory.

The workload of electrophysiological procedures has steadily increased in our tertiary referral centre. Over 1000 patients have been treated in the past 20 years and it is projected that 219 new patients will be treated in 1991 and 342 procedures will be carried out. Over 25% of patients now receive either catheter or surgical ablation and almost 80% of these are cured permanently without the need for further drug treatment. The development of safer techniques for catheter ablation has led to its increased use and a decline in surgical ablations. Because catheter ablation is a much simpler and less traumatic procedure than surgical ablation there are great advantages both for the patient and in terms of cost-effectiveness. Antitachycardia pacing, relatively common in 1985, has now largely been supplanted by ablation and implantation of defibrillators.

As the tendency to non-pharmacological treatment increases and evidence mounts that cost-effectiveness is greater for electrophysiological treatments, the implications for the funding of electrophysiology services grow. The initially high cost of curative treatment needs to be balanced against the longer term and potentially higher costs of palliative drug treatment. The potential to cure patients with catheter procedures may lead to a greater demand for this expertise and a need for an increase in training and facilities.

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The investigation of cardiac arrhythmias was revolutionised by the introduction of invasive electrophysiological (EP) methods in the late 1960s which clarified mechanisms of arrhythmia and the methods by which accessory pathways and reentrant circuits could be localised. The role of electrophysiological studies became established as a method of confirming the arrhythmia mechanism and substrate, testing antiarrhythmic medications, and as a prerequisite for surgical ablation or implantation of an antitachycardia pacemaker.

Therapeutic options have been extended by the availability of cardiac transplantation and implantable cardioverter-defibrillators. However, because of the advent of catheter ablation in the 1980s[1] the role of the electrophysiological study itself has become extended into a directly therapeutic procedure, with implications for the treatment of a wide variety of cardiac arrhythmias.

We have reviewed the numbers of patients treated by invasive electrophysiological procedures and in particular the trend towards curative treatment and away from drug treatment over the past six years in a tertiary referral centre with a specialist cardiac electrophysiological service.

Methods

The first electrophysiological study was performed in the National Heart and Brompton Hospitals in March 1971. These hospitals functioned as a secondary and tertiary referral centre supplying a wide range of cardiological services to many health authorities. Since 1971 over 1000 patients have undergone more than 1400 invasive procedures for the diagnosis, control, or cure of cardiac arrhythmias. The number remained small until mid 1984, when a full-time clinician with an interest in arrhythmias was appointed. Since then both the number of procedures and the treatments used have grown steadily, though a temporary reduction was seen during 1989–90 when the hospitals amalgamated (to form the Royal Brompton National Heart and Lung Hospital, Chelsea) and laboratory access was temporarily restricted. These restrictions ended in December 1990.

The number and type of invasive electrophysiological procedures performed from 3 March 1971 to 9 May 1991 was obtained from the following sources: (*a*) a computerised database of all catheter laboratory procedures in the Brompton and National Heart Hospitals (currently held in *Orchids** database on an in-house Hewlett Packard 9000 supermini computer); (*b*) a log book of all invasive procedures (maintained by the pacing and electrophysiology physiological measurement technicians); and (*c*) a computerised database of all ablative and implantable device procedures (held in the *EPS*† database on MS-DOS 386 desktop computers).

All data from all sources were coded by a unique hospital number. The data were extracted from the computerised sources and imported into a Lotus 1–2–3 spreadsheet running on a 386-compatible desktop computer. The outcome and complication data for the ablation procedures were provided by in-built report generators in *EPS*.

The types of electrophysiological procedure were classified as follows:

(*a*) *Diagnostic*—To provoke and study mechanisms of clinical arrhythmia and assess the effects of pharmacological or non-pharmacological treatment.

(*b*) *Flutter conversion*—To convert spontaneously occurring atrial flutter.

(*c*) *Antitachycardia pacemaker implant.*

(*d*) *Catheter ablation.*

(*e*) *Surgical ablation.*

(*f*) *Implantable cardioverter defibrillator implant.*

In addition, each procedure was classified as *primary* if performed on a patient who had had no previous invasive electrophysiological procedure of any kind or *secondary* if preceded by an electrophysiological procedure of any kind. Thus most procedures of types (*c*) to (*f*) (above) were secondary, because they were preceded by a diagnostic electrophysiological study. Similarly, restudy after ablation or drug treatment was a secondary procedure. The total number of primary procedures is the same as the number of new patients.

Any secondary procedures carried out at the bedside are not recorded in the sources listed above and are therefore not included in this study. These account for a significant number of repeat electrophysiological procedures carried out on patients undergoing serial electrophysiological-guided drug testing (via single wires left in situ after primary electrophysiological study) and on patients tested after sugical ablation (via epicardial wires placed at operation). We recognise that the number of procedures recorded under "diagnostic electrophysiological study" will be an underestimate.

To place the 1991 workload in the context of previous years, the number of procedures from 1 January 1991 to 9 May 1991 was extrapolated to provide a figure for the whole of 1991, based on the number of working days available in the laboratory and taking into account the possible exaggeration caused by any backlog that had built up by the end of 1990.

Results

ALL ELECTROPHYSIOLOGICAL PROCEDURES

In the 20 year period March 1971—May 1991, 1009 patients had 1428 invasive electrophysiological procedures. Figures 1 and 2 show the annual number of procedures and new patients. The mean number of patients and procedures per year between 1971 and 1983 (inclusive) was 10 and 11 respectively. These figures increased to 110 and 165 between 1984 and the end of 1990, and correspond to the appointment of a full-time cardiac electrophysiologist. At the time of writing, we project that in 1991, after the opening of a dedicated laboratory, we will treat 219 new patients and undertake 342 procedures.

Before 1984 all electrophysiological procedures were diagnostic with the exception of two antitachycardia pacemaker implants. Catheter ablation was introduced in 1984, surgical ablation and flutter conversion in 1985, and an implantable defibrillator implant in 1988. Antitachycardia pacemaker implants were increased from 1985 onwards. Figure 3 shows the breakdown of the total electrophysiological procedures into the six specific types. Table 1 shows the data for primary and secondary procedures in these types.

ABLATIVE PROCEDURES: NUMBERS

Figure 4 shows the percentage of new patients undergoing all ablative procedures since their introduction. This increased steadily from 1985, until ablative procedures represented >30% of all procedures in 1989 and 1990. In 1991 the figure dropped to just under 25%. Inspection of aggregate figures in table 1 showed that the total number of ablations continued to rise in 1991, but there was a drop in diagnostic electrophysiological studies in 1989–90 with no decrease in ablative procedures.

Figure 5 shows the numbers of catheter and surgical ablations. Although it was introduced to these hospitals a year earlier, catheter ablation was rapidly overtaken by surgical ablation from 1985 to 1988. In 1988, the number of surgical ablations was nearly double the number of catheter ablations. There was a sharp reversal from 1989 to the present day, with increasing numbers of catheter procedures at the expense of surgical ablations. At present, there are three times as many catheter ablations as surgical ablations.

Catheter ablation of ventricular tachycardia remains at a relatively low level (a total of 21 procedures between 1985 and the end of 1990) like surgical ablations of ventricular tachycardia in the same period.[20] In contrast, ablation of supraventricular tachycardia has become increasingly successful with catheter techniques, and we project that 48 procedures will

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**Orchids* (Oracle-based Relational Cardiology Hospital Information Database System) is a distributed relational database developed to run under Oracle by Dr A F Rickards at the Royal Brompton National Heart and Lung Hospital. It can run on mainframe, mini, or personal computers. Currently, Orchids covers all in-patient cardiological data with the exception of invasive electrophysiological procedures, which is a planned future expansion.

†*EPS* is a stand alone relational database running on individual desktop computers. It was developed under Dataease by Dr A D Cunningham at the Royal Brompton National Heart and Lung Hospital and can transfer data to *Orchids* if necessary. It allows storage of overview data for all invasive electrophysiological procedures, with in depth modules covering catheter and surgical ablation.

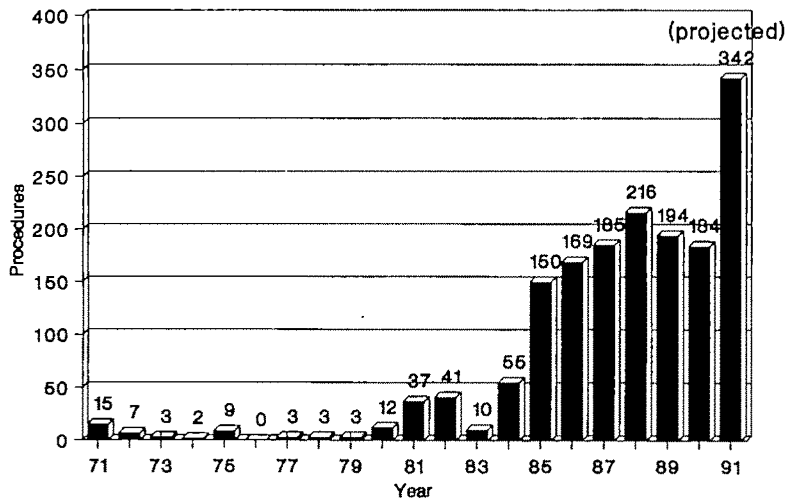


Figure 1 Annual number of procedures between 1971 and 1991. There was a considerable increase after the appointment of a full-time electrophysiologist in 1984. Figures for 1991 are projected from current workload.

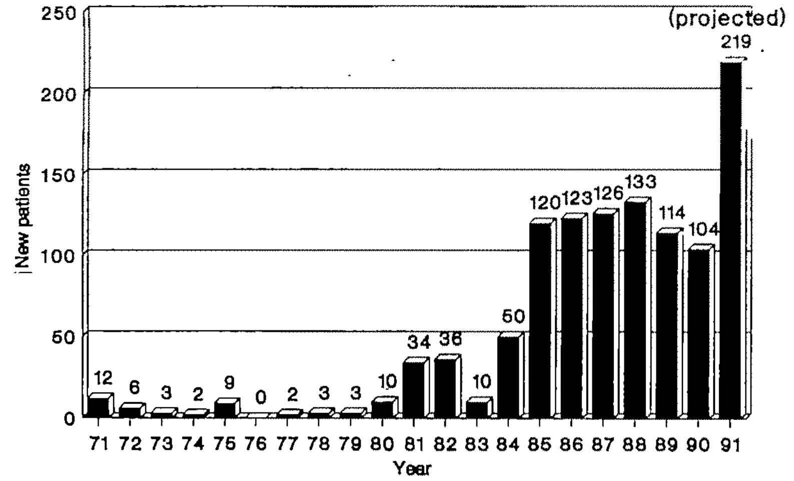
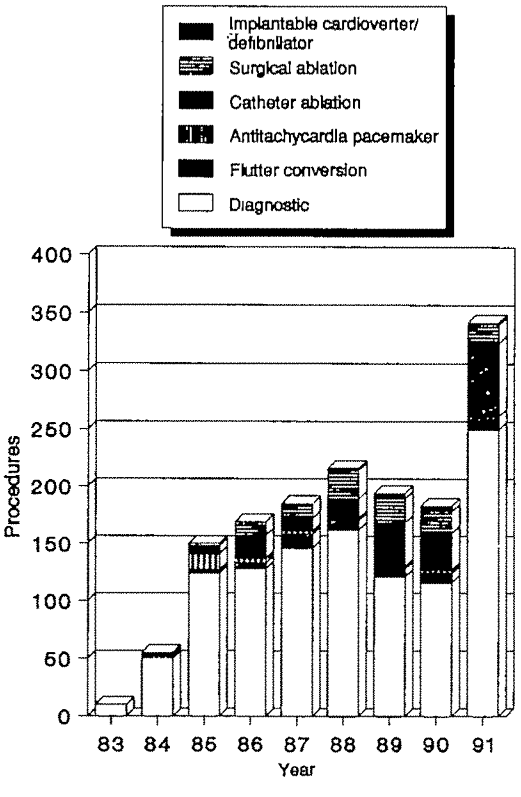


Figure 2 Number of patients per year treated for the first time with invasive electrophysiological procedures. Workload increased steadily since 1984 apart from artificial restrictions in 1989–90 (see text).

Figure 3 Breakdown of procedures from 1983 to 1991 shows the steady rise in catheter ablations, the increase in antitachycardia pacemakers and sugical ablations from 1985 to 1988 which has now been reversed, and the slow emergence of implantation of cardioverter/defibrillators.



be performed by a catheter technique in 1990 compated with 16 by a surgical one. This compares with eight catheter and 23 surgical procedures in 1988.

OTHER FORMS OF NON-PHARMACOLOGICAL TREATMENT

Antitachycardia pacing was at its peak in 1987–89, and was used almost exclusively as a treatment for atrioventricular nodal reentrant tachycardia. Only one patient has had a device implanted since 1989. (This was a patient with slow ventricular tachycardia which could not be ablated by catheter. Because the patient was not a suitable candidate for any surgical procedure owing to very poor left ventricular function, the pacemaker was implanted as a last resort. The patient's ventricular tachycardia was controlled but he died of progressive heart failure nine months later.) Since 1988, implantable cardioverter/defibrillators have increased slowly. A total of 13 patients have currently been implanted with 14 devices.

Two patients in our series received a cardiac transplantation for severe cardiomyopathy complicated by intractable ventricular tachycardia and ventricular fibrillation.

PATIENT FLOW

Figure 6 shows the treatment received by the 1009 patients who underwent invasive electrophysiological procedures: 776 were either treated with drug treatment alone or did not require treatment. The remaining 233 had some form of interventional procedure. There is a complex flow of patients between the forms of non-pharmacological treatment, but several points are worthy of note.

(*a*) Forty one patients were referred directly for catheter ablation without a primary diagnostic electrophysiological study. Most of these underwent ablation of atrioventricular conduction for control of drug-refractory atrial fibrillation or flutter.

(*b*) In the last year, however, an increasing number of patients have had a diagnostic electrophysiological study for atrioventricular nodal reentrant tachycardia or atrioventricular reentrant tachycardia and have progressed immediately to catheter ablation.

(*c*) Sixty nine patients were referred for catheter ablation after a primary electrophysiological study and two had a flutter conversion procedure before catheter ablation.

(*d*) Of 114 patients referred for catheter ablation, 13 (11%) subsequently underwent surgical ablation.

(*e*) Two patients who underwent surgical ablation before 1990 have recently had catheter ablations. One had successful surgical ablation of ventricular tachycardia but after 18 months presented with a new clinical ventricular tachycardia which was successfully ablated by catheter. The second patient initially had an excellent result after surgical ablation of an anteroseptal accessory pathway and simultaneous cryosurgical modification of a slow atrioventricular nodal pathway for cure of atrioventricular nodal reentrant tachycardia. Atrial flutter then occurred three months

Table 1 Annual workloads for invasive electrophysiology procedures

	Diagnostic		*Flutter conversion*		*Antitachycardia pacemaker*		*Catheter ablation*		*Surgical ablation*		*ICD implant*	
Year	*1°*	*2°*	*1°*	*2°*	*1°*	*2°*	*1°*	*2°*	*1°*	*2°*	*1°*	*2°*
pre-1984	130	7	0	0	5	3	0	0	0	0	0	0
1984	50	0	0	0	1	1	3	0	0	0	0	0
1985	115	9	3	0	8	6	7	0	2	0	0	0
1986	113	15	4	1	3	1	13	7	12	0	0	0
1987	113	33	11	1	3	0	8	3	13	0	0	0
1988	122	40	6	2	2	0	13	4	25	0	2	0
1989	95	26	6	1	2	0	27	11	21	0	5	0
1990	90	26	7	1	3	0	25	7	19	0	4	1
1991 (projected)	192	58	11	0	0	0	50	13	16	0	2	0

1°, primary procedure; 2°, secondary procedure; ICD, implantable cardioverter/defibrillator.

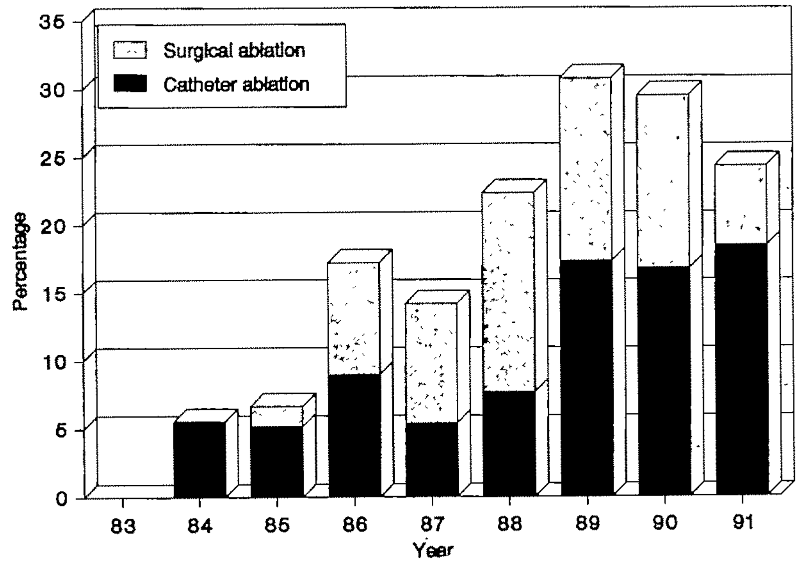


Figure 4 Percentage of patients undergoing definitive ablative treatment increased from zero in 1983 to 30% in 1989–90. Number of procedures continues to increase in 1991, although an increase in diagnostic electrophysiological studies reduced the proportion of ablative procedures to 25%.

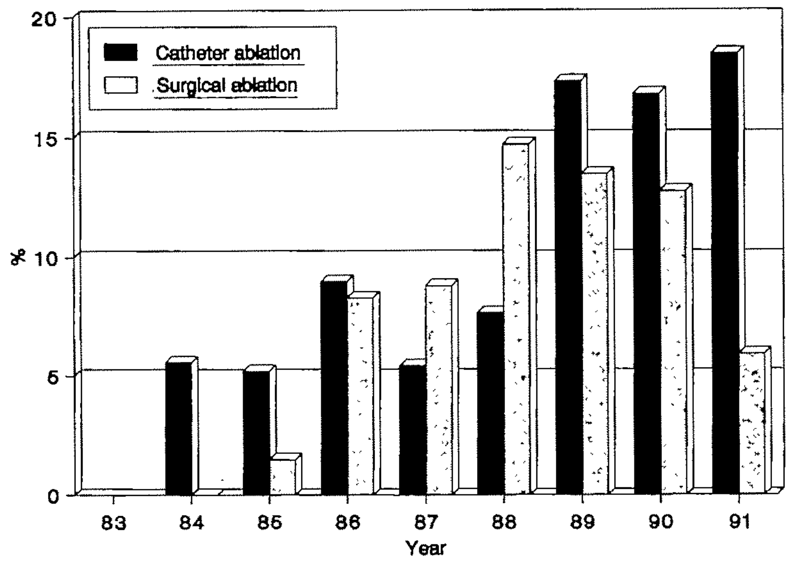


Figure 5 Relative number of patients undergoing catheter or surgical ablation shows surgical procedures overtaking catheter procedures from 1985 to 1988 and then a progressive decline in surgical procedures accompanied by a sharp rise in catheter ablations.

postoperatively, and was conducted via the single remaining atrioventricular nodal pathway with intermittent 1 : 1 response. Because the patient remained refractory to medication, catheter ablation was used to create complete heart block. A further patient who failed surgical ablation of an accessory pathway at another United Kingdom centre has also had successful catheter ablation recently.

(*f*) Of the 12 patients receiving implantable cardioverter/defibrillators, 10 were referred direct from diagnostic electrophysiological study, one had a failed catheter ablation, and one a failed surgical ablation.

(*g*) Seven hundred and seventy six patients (77%) were managed by drug treatment alone or required no treatment. Many of these patients underwent serial electrophysiological testing, although some of these procedures were carried out at the bedside via a single wire left in situ after the primary electrophysiological study. These bedside studies are not included in the procedure numbers in fig 6.

ABLATIVE PROCEDURES: RESULTS

One hundred and ninety seven patients had one or more ablative procedures. Ninety nine had 1–4 catheter ablation sessions; 83 had a single surgical ablation session; 13 had surgical ablation after failed catheter ablation; and two had catheter ablation after previous surgical ablation, as discussed above. The overall results were complete cure in 155 (79%), control of arrhythmia by a previously ineffective drug treatment in 10 (5%), failure in 28 (14%), and procedure-related death in three (1·5%) (table 2).

Tables 3 and 4 show the individual results for catheter and surgical ablation of different arrhythmias. Overall, catheter ablation was successful in 59%, with minimal complications. Surgical ablation had a higher success rate (89%) but there were serious complications in 10%. All three surgical failures to divide accessory pathways occurred within the first two years of experience. No patients required a repeat surgical ablation whereas multiple catheter ablation sessions were required in 25·4% of patients.

Discussion

FACTORS AFFECTING TOTAL NUMBER OF ELECTROPHYSIOLOGICAL PROCEDURES

As one would expect, there was a major

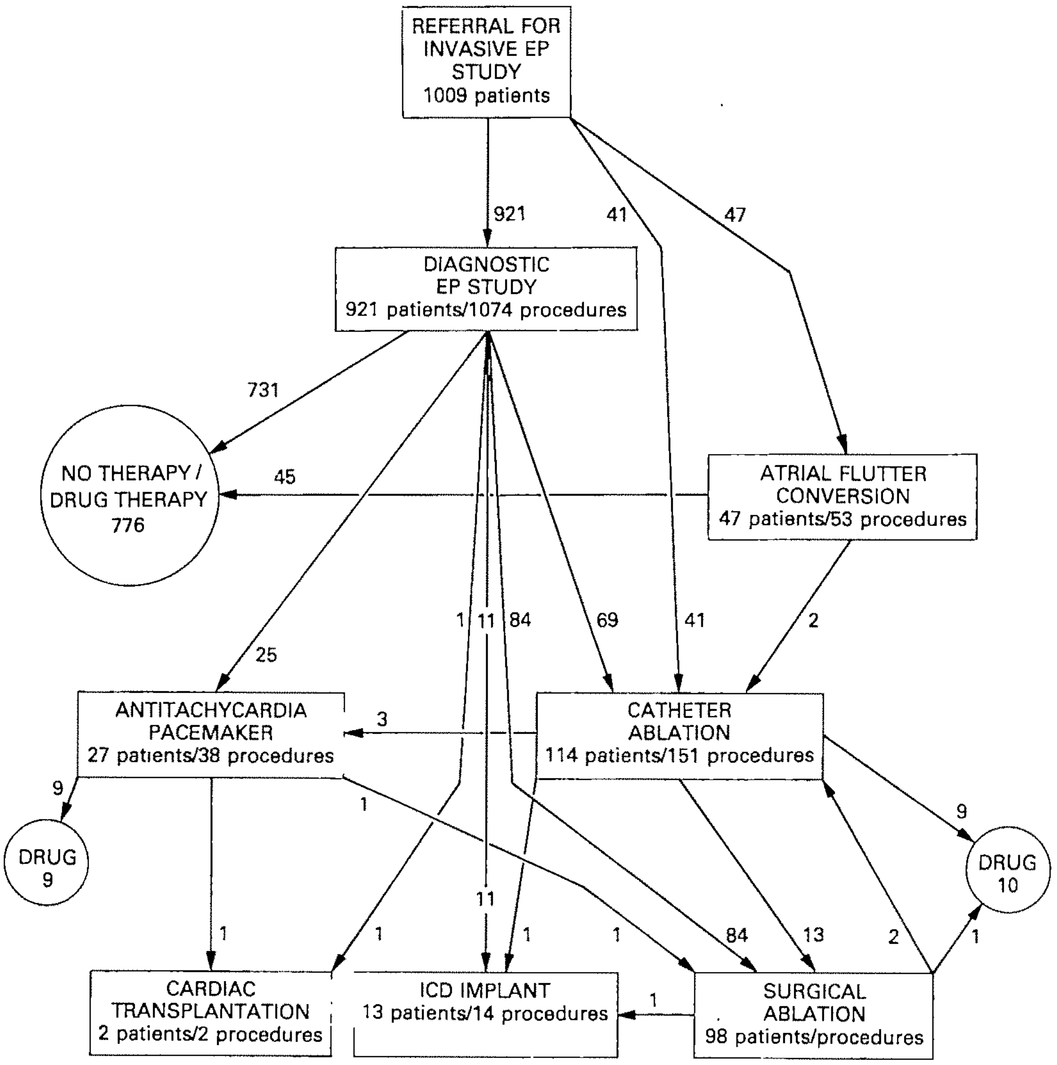


Figure 6 Flow of 1009 patients undergoing 1428 invasive electrophysiological procedures over a 20 year period shows that most patients require no treatment or only drug treatment. However, an increasing number receive non-pharmacological treatment, in particular ablative procedures. Most of these have had a prior diagnostic electrophysiological study, but there is a recent trend towards combining the two into a single study. This is both convenient for the patient and highly cost-effective. Antitachycardia pacemakers are no longer used, having been replaced by ablation and implantation of a cardioverter/defibrillator.

increase in the number of electrophysiological procedures after a full-time cardiac electrophysiologist was appointed midway through 1984. There has also been a progressive increase in total procedures since that time because of increasing clinical demand.

IMPLANTABLE DEVICES

Antitachycardia pacing was at its peak in 1985–87 and was used almost exclusively as a treatment for atrioventricular nodal reentrant tachycardia. Since that time, surgical and then catheter techniques have increasingly offered a potential cure for this arrhythmia and have now completely supplanted the use of antitachycardia pacing in our hospital. In patients with ventricular arrhythmias that cannot be controlled by drugs or cured by an ablative procedure, the implantable cardioverter/defibrillator, with or without an antitachycardia pacing capability, offers a much more secure treatment than antitachycardia pacing alone, because of risk of tachycardia acceleration. (Many of the present generation of "tiered-therapy" implantable cardioverter/defibrillator devices incorporate antitachycardia pacing modes as the primary treatment for haemodynamically tolerated ventricular tachycardia, and the future role of the stand alone antitachycardia pacemaker is therefore probably very small in centres such as ours.)

ABLATIVE PROCEDURES

Table 2 shows that nearly 80% of patients who were treated by catheter and/or surgical ablation were completely cured without the need for drug treatment. Catheter ablation was used with enthusiasm in its early stages, but some disillusionment with poor results led to its partial decline in 1987–88, as shown by the relatively higher number of surgical ablations at that time (fig 5). However, improvements in

Table 2 Overall results of ablative procedures

Procedure	*Number of of patients*	*Cured (%)*	*Controlled by previously ineffective drug treatment (%)*	*Failed (%)*	*Procedure-related death (%)*
Catheter ablation alone	99	66 (67)	9 (9)	24 (24)	0
Catheter then surgical ablation	13	9 (69)	1 (8)	1 (8)	2 (15)
Surgical ablation alone	83	78 (94)	0	3 (4)	2 (2)
Surgical then catheter ablation	2	2 (100)	0	0	0
Total	197	155 (78·7)	10 (5·1)	28 (14·2)	4 (2·0)

Table 3 Results of catheter ablation

Procedure	*Number of of patients*	*Cured*	*Controlled by previously ineffective drug treatment*	*Failed*	*Procedure-related death (%)*
Accessory pathway	38	21	4	13	0
Ventricular tachycardia	15	5	3	7	0
Atrial tachycardia	2	0	0	2	0
Ablation of AV conduction	52	40	3	9	0
Modification of AV conduction	5	1	0	4	0
Atrial flutter	2	0	0	2	0
Total	114	67 (58·8%)	10 (8·8%)	37 (32·5%)	0

Serious complications (3): coronary sinus rupture (1) (after high energy catheter ablation of posteroseptal accessory pathway in the coronary sinus os. Surgically repaired in catheter laboratory) and ventricular fibrillation (2). AV, atrioventricular.

Table 4 Results of surgical ablation

Procedure	*Number of of patients*	*Cured*	*Controlled by previously ineffective drug treatment*	*Failed*	*Procedure-related death (%)*
Accessory pathway	68	64	0	3	1
Ventricular tachycardia	20	14	1	3	1
Atrial tachycardia	4	3	0	0	0
Ablation of AV conduction	4	3	0	0	1
Modification of AV conduction	2	2	0	0	0
Total	98	87 (88·8%)	1 (1·0%)	6 (6·1%)	3 (2·9%)

Serious complications (10): procedure-related death (3) (low output state after bypass (2 h) followed by accessory pathway ablation, progressive cardiac failure (3 days) followed by VT ablation, septicaemia (7 days) followed by ablation of AV conduction); late deaths (1) (sudden cardiac death (6 months) followed by VT ablation); severe CVA (2); complete heart block after accessory pathway dissection (1); acute congestive heart failure (1); atrial flutter with 1:1 atrioventricular conduction (1); right leg amputation (1).
AV, atrioventricular, VT, ventricular tachycardia; CVA, cerebrovascular accident.

technology (the development of a low-energy ablation power source[2] and catheter[3] and technique (particularly the use of retrograde aortic catheterisation to approach left sided accessory pathways[4] led to improved results and increased enthusiasm from 1989 onwards. As a result, catheter ablation procedures in the past three years have had a success rate approaching 80% and now outnumber surgical ablations 3 : 1. Such a ratio is likely to persist or even increase as ablation methods which do not require a general anaesthetic (such as radiofrequency[5]) are increasingly used. Radiofrequency ablation was introduced in our hospital in 1990, and our early results suggest that its success rate is comparable to low or high energy DC ablation for accessory pathway ablation. Other workers' experience[6] suggests that it may be a less useful technique for the creation of a complete heart block or ablation of ventricular tachycardia, but it is probably the technique of choice[6,7] for *modification* of the atrioventricular node in cases of atrioventricular nodal reentrant tachycardia.

Early on, when we were using high energies and conventional pacing catheters for ablation, cardiac tamponade was caused in one patient by rupture of the coronary sinus during attempted ablation of a posteroseptal accessory pathway. This experience and similar reports from other groups gave us the impetus to develop safer methods of catheter ablation.[2,3] Our fundamental strategy is to err on the side of safety during catheter ablation, thus making it a safe and reasonably effective procedure, and therefore worth attempting before proceeding to operation in almost all patients. In our practice, it is the treatment of choice for ablation of accessory pathways as well as for the creation of complete heart block, and it remains worth attempting in some selected cases of ventricular tachycardia. Surgical treatment has been preferred to catheter modification of atrioventricular nodal conduction in the treatment of atrioventricular nodal reentrant tachycardia and for ablation of focal atrial ectopic tachycardia. We have, however, begun to gain experience in attempting modification of atrioventricular nodal conduction by multiple applications of radiofrequency energy to the region of the triangle of Koch. Other groups have already reported success with this technique, both with radiofrequency energy[7,8] and conventional shocks.[9] Recently reported results for ablation of accessory pathways by radiofrequency energy[8,10,11] suggest that this technique may completely replace surgery for this indication in the near future.

COST EFFECTIVENESS OF CATHETER ABLATION

Significant decreases in health care costs have been reported during long-term follow up of patients who have undergone catheter ablation of atrioventricular conduction[12,13] or an accessory pathway.[14] The number of hospital admissions was greatly reduced and the need for drug treatment was virtually eliminated. Although similar long-term studies have not been reported for catheter ablation of accessory pathways, one would expect even greater savings in these patients because a permanent pacemaker is not required.

Used as described above, we believe that catheter ablation is an extremely valuable, minimally traumatic, and cost-effective tool for the management of arrhythmias. Because the option of surgical ablation is available we can use catheter ablation with caution, maximising its safety and allowing it to be used not only as a treatment of last resort.

PHARMACOLOGICAL TREATMENT VERSUS NON-PHARMACOLOGICAL TREATMENT

Most (77%) patients in this study required no treatment or received drug treatment alone, guided by serial electrophysiological testing where appropriate. However, this global figure masks a trend away from pharmacological treatment over the past few years, and over 30% of patients now receive one or other form of non-pharmacological treatment. Increasingly we are turning away from pharmacology and towards attempting to cure arrhythmias with ablation or to palliate them with devices that we hope are more cost-effective than drug treatment. It is unfortunate that we are not in a position to compare the efficacy and cost-effectiveness of pharmacological and non-pharmacological treatments, and it will be a prime requirement to attempt to make such judgements when our new information systems are in place. Meanwhile, resource limitations (both in terms of laboratory time and device funding) will be the principal limitation on our use of non-pharmacological treatment strategies. The present data indicate that the limit lies at around 30–35% of all patients referred for invasive electrophysiological study.

Clearly drug treatment may be more expensive over the lifetime of a patient but the expense is spread out over years. Non-pharmacological treatment, particularly device implantation, is much more expensive initially and then much less expensive as time goes by. It is therefore more cost-effective if the patient survives for a long period, but the initial outlay is much greater and provision for costing and comparing such contrasting treatments needs to be made to enable referring physicians to make an informed and sensible choice.

ELECTROPHYSIOLOGICAL PROCEDURES IN THE CONTEXT OF GENERAL CARDIOLOGICAL CARE

It would have been interesting to examine the referral patterns of patients for invasive electrophysiological procedures within our hospitals and their relation to the advances in treatment and also to the clinical outcome of these patients; however, with the exception of patients who had ablation, antitachycardia pacemakers and implantable cardioverter/defibrillators, clinical outcome data were not available, nor were retrospective referral patterns. All of these data will be available prospectively, however, with the introduction of new administrative and clinical computing systems in 1990–92; it will then be possible to assess the true impact on clinical outcome, quality of life, and cost-effectiveness of different treatments for cardiac arrhythmia.

Until then this present review indicates that the demand for invasive electrophysiological procedures within our hospitals continues to increase, and the resumption of this increase in 1991 after artificially imposed restrictions in 1989–90 shows little tendency for the curve to flatten out. It may well be that the clinical need for these procedures exceeds the services provided nationally in the United Kingdom and that the number of procedures that we are able to perform will therefore always remain resource-limited. If that is the case, and provided cost-effectiveness can be demonstrated, then consideration should be given to increasing the availability of these services, both by training more cardiac electrophysiologists and by providing a larger number of specialist centres with facilities to provide all of these treatments.

1 Scheinman MM, Morady F, Hess DS, Gonzalez R. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. *JAMA* 1982;248:851–5.
2 Cunningham D, Rowland E, Rickards AF. A new low energy power system for catheter ablation. *PACE* 1986;9: 1384–90.
3 Ahsan AJ, Cunningham D, Rowland E, Rickards AF. Catheter ablation without fulguration: design and performance of a new system. *PACE* 1989;12:1557–61.
4 Warin J-F. Catheter ablation of accessory pathways: technique and results in 248 patients. *PACE* 1990;13:1609–14.
5 Huang SK, Bharati S, Graham AR, Lev M, Marcus FI, Odell RC. Closed-chest catheter ablation of the atrioventricular junction using radiofrequency energy: a new method of catheter ablation. *J Am Coll Cardiol* 1987;9:349–58.
6 Cunningham D. High energy catheter ablation of cardiac arrhythmias: an outmoded technique in the 1990s. *Clin Cardiol* 1991;14:595–602.
7 Lee MA, Morady F, Kadish A, *et al.* Catheter modification of the atrioventricular junction with radiofrequency energy for control of atrioventricular nodal reentry tachycardia. *Circulation* 1991;83:827–35.
8 Calkins H, Sousa J, El-Atassi R, *et al.* Diagnosis and cure of the Wolff-Parkinson-White syndrome or paroxysmal supraventricular tachycardia during a single electrophysiological test. *N Engl J Med* 1991;324:1612–8.
9 Haissaguerre M, Warin JF, Lemetayer P, Saoudi N, Guillem JP, Blanchot P. Closed-chest ablation of retrograde conduction in patients with atrioventricular nodal reentrant tachycardia. *N Engl J Med* 1989;320: 426–33.
10 Jackman WM, Wang X, Friday KJ, *et al.* Catheter ablation of accessory atrioventricular pathways (Wolff–Parkinson–White syndrome) by radiofrequency current. *N Engl J Med* 1991;324:1605–11.
11 Kuck K-H, Schlüter M, Geiger M, Siebels J, Duckeck W. Radiofrequency current catheter ablation of accessory atrioventricular pathways. *Lancet* 1991;337:1557–61.
12 Kay GN, Bubien RS, Epstein AE, Plumb VJ. Effect of catheter ablation of the atrioventricular junction on quality of life and exercise tolerance in paroxysmal atrial fibrillation. *Am J Cardiol* 1988;62:741–4.
13 Rosenqvist M, Lee MA, Moulinier L, *et al.* Long-term follow-up of patients after transcatheter direct current ablation of the atrioventricular junction. *J Am Coll Cardiol* 1990;16:467–74.
14 de Buitleir M, Bove EL, Schmaltz S, Kadish AH, Morady F. Cost of catheter versus surgical ablation in the Wolff–Parkinson–White syndrome. *Am J Cardiol* 1990;66: 189–92.

Br Heart J 1992;67:106–16

Provision of services for the diagnosis and treatment of heart disease

Fourth Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England

Abstract

The principal conclusions of the fourth report of the Joint Cardiology Committee are:

1 Cardiovascular disease remains a major cause of death and morbidity in the population and of utilisation of medical services.

2 Reduction in the risk of cardiovascular disease is feasible, and better co-ordination is required of strategies most likely to be effective.

3 Pre-hospital care of cardiac emergencies, in particular the provision of facilities for defibrillation, should continue to be developed.

4 There remains a large shortfall in provision of cardiological services with almost one in five district hospitals in England and Wales having no physician with the appropriate training. Few of the larger districts have two cardiologists to meet the recommendation for populations of over 250 000. One hundred and fifty extra consultant posts (in both district and regional centres) together with adequate supporting staff and facilities are urgently needed to provide modest cover for existing requirements.

5 The provision of coronary bypass grafting has expanded since 1985, but few regions have fulfilled the unambitious objectives stated in the Third Joint Cardiology Report.

6 The development of coronary angioplasty has been slow and haphazard. All regional centres should have at least two cardiologists trained in coronary angioplasty and there should be a designated budget. Surgical cover is still required for most procedures and is best provided on site.

7 Advances in the management of arrhythmias, including the use of specialised pacemakers, implantable defibrillators, and percutaneous or surgical ablation of parts of the cardiac conducting system have resulted in great benefit to patients. Planned development of the emerging sub-speciality of arrhythmology is required.

8 Strategies must be developed to limit the increased exposure of cardiologists to ionising radiation which will result from the expansion and increasing complexity of interventional procedures.

9 Supra-regional funding for infant cardiac surgery and transplantation has been successful and should be continued.

10 Despite advances in non-invasive diagnosis of congenital heart disease the amount of cardiac catheterisation of children has risen due to the increase in number of interventional procedures. Vacant consultant posts in paediatric cardiology and the need for an increase in the number of such posts cannot be filled from existing senior registrar posts. All paediatric cardiac units should have a senior registrar and in the meantime it may be necessary to make proleptic appointments to consultant posts with arrangements for the appointees to complete their training.

11 Provision of care for the increasing number of adolescent and adult survivors of complex congenital heart disease is urgently required. The management of these patients is specialised, and the committee recommends that it should ultimately be undertaken by either adult or paediatric cardiologists with appropriate additional training working in supra-regionally funded centres alongside specially trained surgeons.

12 Cardiac rehabilitation should be available to all patients in the United Kingdom.

13 New recommendations for training in cardiology are for a total of at least five years in the specialty after general professional training, plus a year as senior registrar in general medicine. An additional year may be required for those wishing to work in interventional cardiology and adequate provision must be made for those with an academic interest.

14 It is essential that both basic and clinical research is carried out in cardiac centres but these activities are becoming increasingly limited by the lack of properly funded posts in the basic sciences and restriction in the number of honorary posts for clinical research workers.

15 A joint audit committee of the Royal College of Physicians and the British Cardiac Society has been established to

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BL Pentecost (chairmen)
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A T Bevan
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coordinate audit in the specialty. All district and regional cardiac centres should cooperate with the work of the committee, in addition to their participation in local audit activities.

1 Introduction

1.1 The third report of the Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England (1985) anticipated several imminent developments in the diagnosis and treatment of heart disease and recommended a further review within five years.[1]

1.2 In preparing this fourth report the committee sought to assess the extent to which the recommendations of 1985 have been realised and to discuss present and future needs in the light of that progress and the projected burden of heart disease in the United Kingdom over the next decade.

1.3 The overall assessment is one of, at best, hesitant progress towards implementation of the earlier objectives. The crucial role of the cardiologist practising in the district general hospital was widely acknowledged even before the time of the third report, but gross underprovision of cardiological services continues to exist in many parts of the country. Within the regional specialist centres the use of coronary angioplasty and other interventional procedures has expanded, though more slowly than in mainland European countries and North America. The provision of coronary artery surgery has also failed to achieve the unambitious 1985 minimum targets in all but a few regions. Of other "high technology" developments anticipated in 1986 prenatal diagnosis of congenital heart disease has continued to evolve and magnetic resonance imaging has fulfilled much of its promise but remains confined to a few centres. An anticipated requirement for intracoronary thrombolysis has been overtaken by demonstration of the practical superiority of intravenous therapy. Major new developments are required to care for the increasing number of adults with partially corrected or uncorrectable congenital heart disease and to exploit recent advances in the treatment of arrhythmias.

2 Scale of the problem

2.1 Well over a quarter of a million people die every year from diseases of the circulatory system in England and Wales. These diseases are the most frequent cause of death in both sexes and account for approximately half of all deaths. Cardiovascular diseases account for 26% of all years of working life lost in men (to age 65) and 15% of those lost in women.[2]

2.2 The major cause is coronary heart disease which accounts for 65% of cardiovascular deaths in men and 49% in women.[3] About one in 200 men die of coronary heart disease before the age of 45 and this increases to one in 11 men before the age of 65. For women up to the age of 65 coronary heart disease claims the lives of about one in 40. These rates are among the highest in the world, and though they reflect a fall since 1978 they remain 50% above the 1950 level.[4] The United Kingdom has yet to experience the large general decline in deaths from coronary heart disease which North America and several European countries have been enjoying for some years. A major logistical problem hindering the effective delivery of aid relates to the time and place of these deaths: about half are sudden and most occur within the home. Although all areas of the United Kingdom have high levels of coronary heart disease, wide differences exist between regions and social classes: Glasgow has twice the death rate of some parts of London and within each region higher death rates are associated with manual workers and the lower paid.

The principal burden on the cardiological services, however, is imposed by the high prevalence of coronary heart disease in the community. The British Regional Heart Study showed that in the early 1970s 25% of men aged 40–59 had some evidence of coronary heart disease.[5 6] In the Welsh Heart Health Survey of 1985 18% of men and 11% of women aged 55–64 had a history of myocardial infarction, and/or symptoms of angina, and/or electrocardiographic changes of myocardial infarction.[7] If these prevalence rates applied to the whole United Kingdom population some two million people under the age of 64 would have evidence of coronary heart disease. While much of this disease may be clinically unrecognised, it was estimated that in 1984 ischaemic heart disease was responsible for 2·43 million bed days in English hospitals.[8]

2.3 Chronic rheumatic heart disease is now an infrequent cause of death and morbidity in Britain, but degenerative valve disease remains an important cause of hospital admission for treatment of heart failure and for surgery; the number of affected patients is likely to rise with the increasing number of elderly people in the population. Studies of general practice and hospital admissions in London found that the prevalence of heart failure in the community rose from six per 10 000 under the age of 65 to 280 per 10 000 over 65. Coronary artery disease was the predominant aetiology with valve disease reponsible for 13% of cases and hypertension (6%), cor pulmonale (3%), and congenital heart disease (2%) as other identifiable causes. Underuse of diagnostic procedures resulted in a significant proportion of cases (37%) in which an aetiology could not be accurately established.[9]

2.4 Deaths in infancy and childhood from congenital heart disease have also declined, chiefly because of the benefits of medical treatment and surgery. The birth rate in the United Kingdom has been static over the last four years, according to Department of Health figures. Since the incidence of congenital heart disease (eight per 1000 live births)[10] is unchanged, there is no evidence of naturally declining numbers to account for the reduction in deaths. Many adolescent and adult survivors of congenital heart disease, however, require specialised follow up and make heavy demands on the hospital services (see 8).

3 Prevention

3.1 Abundant evidence testifies to the importance of environmental factors in the genesis of cardiovascular disease. This has been derived from international and within country comparisons, the effects of migration, and community intervention projects. The concept that risk can be reduced by appropriate modifications of life style is therefore realistic and supported by recent controlled trials.[11] We recognise that achievements in this area have sometimes been disappointing. We do not doubt, however, that improved identification of strategies that may be potentially successful and more urgent emphasis on those that are most firmly established can have an important impact.

3.2 The recommendations published in 1987 by the British Cardiac Society[12] form a useful basis for action by doctors with a special interest in and responsibility for the control of heart disease. Government leadership, however, is essential: as yet no strategy for coronary prevention has been developed and action has been piecemeal. Many government and European Community policies run counter to coronary risk reduction and the achievement of good health.[4] Contributions from the regional and district health authorities and the education services have been slow to develop. These deficiencies need to be addressed.

3.3 The British public continues to consume excessive quantities of fat, especially saturated fat. This should be reduced, with approximately equivalent quantities of saturated, monounsaturated, and polyunsaturated fat being eaten. Physicians in general and cardiologists in particular should encourage dietary change of this kind. Cholesterol measurement is of value in identifying some people at high risk who may benefit from special dietary regimens or drug therapy. Cholesterol testing should be directed to those with a family history of premature coronary disease or with clinical features of hyperlipidaemia, those with manifest coronary disease (especially after bypass grafting or angioplasty), those under treatment for diabetes and high blood pressure, and those with a long history of heavy smoking.[13]

3.4 Blood pressure screening is already commonplace in general practice and occupational health services, and its importance has been stressed in the recent government white paper on the reorganisation of the National Health Service.[14 15] The beneficial effects of the lowering of raised blood pressure by drug therapy on the incidence of stroke and cardiac failure are undoubted. There may also be a significant although smaller reduction in the incidence of coronary heart disease.[16]

3.5 Strenuous efforts should be made to counter the harmful effects of smoking on cardiovascular health. It is the single most important risk factor for coronary heart disease and one that is self inflicted and entirely preventable.[17] The government is in a unique position to reduce cigarette smoking by imposition of higher tax, tougher restriction of advertising and sponsorship by tobacco companies, and designation of funds for education.

4 Pre-hospital treatment of cardiac emergencies

4.1 In Britain approximately two thirds of deaths from coronary heart disease occur outside hospital, often within one hour of the onset of symptoms and usually from ventricular fibrillation.[18] Many lives could be saved every year if the urgency of prompt care were widely appreciated. The advent of thrombolysis has further increased the need for early medical intervention in patients with acute myocardial infarction.

4.2 Equipment for and expertise in defibrillation should be available outside hospital, particularly in areas such as sports stadiums and airports where large numbers of people are likely to assemble.[19] It can be provided by general practitioners, but in many areas will be delivered most effectively by ambulance personnel who should ideally also have training in airway control, intravenous infusion, and the use of cardioactive drugs. In the short term, ambulance staff and first aid workers with basic training can be instructed within a few hours in the use of advisory defibrillators and can save life.[20] The key to successful defibrillation is a short response time and this should be the major factor in determining the best system for a particular area. Basic cardiopulmonary resuscitation before the arrival of a defibrillator improves survival and the general public should be trained in accordance with Resuscitation Council guidelines.[21] But the success of out-of-hospital resuscitation from cardiac arrest will be negligible if rapid defibrillation is not available. A recent government initiative encouraging the availability of defibrillators in all front-line ambulances is welcome.

4.3 The value of pre-hospital thrombolysis in suspected acute myocardial infarction is unproven but may be clarified by current trials. General practitioners with appropriate expertise who wish to take responsibility for the administration of thrombolytic agents should be supported, especially if they work at a distance from a general hospital, but they must be able to confirm the diagnosis electrocardiographically.

5 The district hospital

CONSULTANT STAFF

5.1 Much of the heart disease in the United Kingdom will present to a cardiologist in a district general hospital who usually has a commitment to the provision of general medical care. Ischaemic heart disease presents the greatest proportion in terms of workload and use of resources, and the district cardiologist has a central role both in prevention and treatment. The increasing awareness and expectations of the public which were noted in the 1985 report continue. In particular, the need—often inadequately met—for intervention in coronary artery and valve diseases has placed mounting pressure on the district cardiologists who are responsible for the initial evaluation. The introduction of coronary thrombolysis has increased the need for skilled evaluation and careful follow up of patients after acute myocardial infarction. The increase in workload, both in scope and in complexity, of the district cardiologist limits the time for more general medical commitments of the appointment. Sessions at the regional cardiac centre can offer advantages that include improved liaison, better upgrading of specialised knowledge and practical skills, continuity of care, and collaboration in follow up after surgery or pacemaker implantation. A divided commitment may, however, be difficult to achieve and should not be undertaken at the expense of the principal responsibilities in the district general hospital.

5.2 A realistic appraisal of the needs of a district hospital, made over three years ago, suggested a requirement for two cardiologists per 250 000 population.[22] It is unfortunate that we are scarcely any closer to this goal than at the time of the last report: of 83 hospitals in this category only 37 have two cardiologists. Indeed even in 1990 no less than 41 of 212 district hospitals in England and Wales lacked any physician with specialised training in cardiology. This deficiency is not confined to smaller health districts.

5.3 The committee reiterates its recommendation (*a*) that fully funded posts in cardiology with adequate facilities are developed in all district hospitals that lack one and (*b*) that urgent consideration be given to the need for two consultant cardiologists in those districts where the population exceeds 250 000 with greatest priority for parts of the country with higher levels of morbidity and mortality from heart disease. The target, however, remains the provision of one cardiologist per 125 000 population. This has long been exceeded in most other western European countries.

5.4 An estimate of the total shortfall in posts (including both district hospitals and centres) agreed by the Manpower Committee of the Royal College of Physicians is 150. Even with this major addition to staffing levels the United Kingdom will still have fewer than 10 posts per million population compared with approximately 45 per million for the rest of Europe.[23]

JUNIOR STAFF

5.5 It is usual for the district cardiologist to have either a registrar or a senior house officer who may be part of a general medical rotation. The more junior doctor will usually be completing general professional training rather than starting a career in cardiology and thus the opportunity to receive more than a superficial training in non-invasive cardiology is limited. In these circumstances the trainee will not be able to contribute fully to the work of the department. This necessarily implies a substantial consultant involvement at all levels of the service although the use of clinical assistant sessions may be a valuable means of providing continuity. The use of the staff grade for certain types of work such as exercise testing may also ease the workload, but this strategy should not deflect attention from the need for more consultant posts.

SUPPORTING STAFF

5.6 Adequate provision of physiological measurement technicians and cardiographers must be made to deal with the needs of routine electrocardiography, ambulatory electrocardiographic monitoring, stress testing, echocardiography, pacemaker implantation where performed, and pacemaker clinics. A figure of seven cardiological physiological measurement technicians per 250 000 population is recommended.[22] The work of cardiological technicians may be integrated with that of other departments in which case additional staffing will be required.

CARDIAC CARE UNIT

5.7 There should be a dedicated cardiac care unit in all district hospitals, with 6–8 monitored beds for the average sized district with a population of 250 000, depending mainly upon the burden of coronary heart disease within the catchment area. The role of the cardiac care unit has expanded and may include the care of any sick cardiac patient requiring continuous monitoring of heart rhythm or haemodynamic variables. The unit should be supervised by the cardiologists who will be responsible for operational policy in agreement with colleagues. There should be facilities for insertion of emergency pacemakers and invasive pressure monitoring; this need implies the availability of image intensification within the unit.

We consider these facilities are necessary for the appropriate designation of a ward area as a cardiac care unit. The availability of monitored beds does not in itself justify this designation.

PROGRESSIVE CARE

5.8 After discharge from the cardiac care unit there are advantages for the patient being moved to a contiguous, progressive care environment. This enhances continuity of care, provides opportunity for extended monitoring (that is, telemetry) for high risk patients, and is helpful both in rehabilitation and teaching. Disadvantages relate mainly to non-involved medical wards which may experience a reduction in the range of their acute care case mix. Provision must be adapted to local circumstances and needs.

6 Regional cardiac centres

STRUCTURE

6.1 The major cardiac centres are staffed by an integrated team of medical, nursing, and technical staff who jointly provide a comprehensive diagnostic and therapeutic service usually to a population of around 1·5–2 million. The limiting factor in the provision of care is the ability to provide an adequate number of surgical procedures for the community served, particularly coronary artery bypass grafts (CABG). The third joint colleges report estimated an annual requirement of 400 to 500 coronary artery bypass grafts or angioplasties per million of the population. A recent study suggests that this figure should apply to coronary artery bypass grafts, with a need for angioplasty in addition[24] (see 6.4). The range reflects differences in the prevalence of coronary artery disease in different parts of the country, which depend both on the incidence of the disease and the age structure of the population. Whereas some clinicians believe this range is an underestimate of need, in practice even this is rarely achieved. A further move towards the target should result in regional centres undertaking up to 1000 coronary bypass procedures annually with surgery for valvar and congenital heart disease in addition. There is no optimum size for cardiac units but the dangers of too large an institution providing "conveyor belt medicine", with a loss of the personal touch, is a potential disadvantage for patients. In some cases it may be preferable to open a second unit in a more populous region rather than risk this development.

SURGICAL SERVICE

6.2 The regional unit serving 1·5–2 million people whould be able to provide between 800 and 1200 operative procedures each year. This workload requires three or four consultant surgeons, a senior registrar, at least two registrars, plus an appropriate senior house officer complement of at least four. The consultant grade in cardiothoracic surgery is expanding at approximately 3% per annum and maintenance of training grade numbers is of critical importance to ensure a steady supply of well trained cardiac surgeons both to complement this expansion and to fill retirement vacancies. Here, it is going to be essential to provide the Joint Planning Advisory Committee with well argued and updated advice on appropriate numbers of senior registrars and registrars to meet the expected expansion in consultant posts. In units with a paediatric cardiac surgical programme additional consultant numbers will be needed and two of the consultants should have had special training in paediatric cardiac surgery and have responsiblity for this aspect of the work.

The number of consultant anaesthetists involved in cardiac surgical programmes varies from one unit to another but a strong case can be made for matching the number of consultant cardiac surgeons with an equal number of consultant anaesthetists and an appropriate number of trainees. This recommendation takes into account and acknowledges the important role of the anaesthetist in preoperative assessment (including necessary involvement in the cardiac catheter laboratory), the lengthy nature of many of the operations, and involvement in postoperative care. It is important that at least two consultant anaesthetists should be able to regard their involvement with the cardiac surgical programme as their prime responsibility, and this is especially so in regard to paediatric cardiac anaesthesia. The role of the anaesthetic staff in the organisation and conduct of patient care in the intensive care unit also varies from one unit to another, but the increasing importance of the anaesthetist in this area needs emphasis, whether overall command of the intensive care unit remains a surgical or a joint responsibility. The successful running of a happy and effective intensive care unit depends upon close cooperation between surgeon, anaesthetist, cardiologist, and nursing staff, and while each unit has to determine its own working practices, a chain of command agreed between the surgical and anaesthetic staff at all levels is imperative. If the intensive care unit is run by an "intensivist", it is necessary to ensure that junior surgical and anaesthetic staff receive appropriate training in this discipline in the same way as would happen if the unit were run either by a surgeon or an anaesthetist or as a joint undertaking.

The cardiac surgical programme has to be supported by a team of perfusionists. For a programme of 1000 cases per year there need to be four qualified perfusionists and one or two in training. The important role of other supporting staff including personal secretaries and operating department assistants should be recognised and proper remuneration provided.

The use of non-medically qualified operating assistants, as widely practised in North America, is currently under review in the form of a pilot study in the United Kingdom. This is seen as a development that could be important in view of the continuing restrictions imposed on the junior staff establishments in most units and of the need to provide surgeons in training with a balanced programme.

The facilities should include the dedicated use of two operating theatres and occasional access to a third. If interference with other surgical disciplines and intermittent interruption of the surgical programme is to be avoided there must be 10 or 12 dedicated intensive care unit beds available, together with an appropriate number of general ward beds to ensure progressive patient care.

With some elective, particularly coronary artery, surgery it may be possible for units to develop a recovery system for selected postoperative patients short of full intensive care. Some have already done so. This can help to relieve some of the pressure on beds in the intensive care unit but such recovery units have to be well organised with appropriate staff and supervision if standards of after care and the safety of the patient are to be protected.

The problem in recruiting and retraining nursing staff also needs emphasis. Rotation through the various departments of a cardiac unit to encourage the development of a pool of experienced staff familiar with all aspects of care for the cardiac patient can optimise their deployment. Wherever possible unification of nursing command should be encouraged and fragmentation of the nursing budget avoided. Measures such as these are seen to be essential if serious impairment of cardiac services, due to future predictable reduction in numbers of nurses, is to be avoided.

MEDICAL SERVICE

6.3 Approximately twice the number of cardiac catheterisation procedures is required to provide diagnostic support for a given number of patients destined for surgery. An effectively run cardiac catheterisation laboratory is capable of investigating 1000 patients per annum, but angioplasty is more time consuming. A major centre therefore needs at least two such laboratories. The size of the investigative facility within the unit will depend among other things on the number of permanent pacemakers implanted. Where this is substantial, an additional suite dedicated to pacing and electrophysiological studies is an effective and economical alternative to the use of a fully equipped catheter laboratory.

Adequate beds should be provided both for investigation of patients and for the care of those admitted with cardiological problems. The beds required for cardiac catheterisation will vary with the proportion of patients investigated as day cases. This is steadily increasing and is to be encouraged but will be influenced by geographical considerations.

Previous reports have emphasised the need for adequate cardiological staffing at consultant grade. We endorse earlier recommendations for a complement of two cardiologists for every cardiac surgeon, which implies a minimum of six for the smallest unit and at least eight in the ideal major regional unit. The expansion of interventional cardiology, notably coronary angioplasty, together with increasing awareness of the hazards of excessive exposure to radiation may dictate the need for even larger numbers. Adjustments might be appropriate if a radiologist or visiting cardiologist is involved in diagnostic and interventional procedures. The cooperation of a cardiologist, however, is strongly recommended for radiologists to undertake coronary angioplasty or balloon dilatation of valves.

As the scope and workload in cardiology increases as much clinical practice as possible should be transferred to the district general hospital. Permanent pacemaking can appropriately be undertaken in district general hospitals provided facilities and expertise are adequate and that cover can be made available if a single-handed cardiologist is absent from the unit. This frees valuable facilities in the major units and is more convenient for patients and professionally rewarding to the district cardiologists.

CORONARY ANGIOPLASTY

6.4 Considerable development in percutaneous transluminal coronary angioplasty (PTCA) has occurred since the previous report. The original indication—resistant angina produced by a discrete single vessel stenosis—has been expanded, and many patients with multivessel and multilesion disease can be treated successfully by PTCA. The technique has a significant role in the management of patients with unstable angina, those with continuing ischaemia after myocardial infarction, and patients who have already had coronary bypass grafts.

PTCA is usually well tolerated, entailing about two to three days in hospital and a quick return to full activity. The risks are low and would be falling but for the widening indications that result in greater hazard from multivessel disease and poor myocardial function. The small mortality—0·4% for single vessel disease in the United Kingdom[25]—is largely related to acute occlusion of the artery during or shortly after the procedure. The immediate success rate for relief of stenoses should be about 90%; that for chronic occlusions is lower. Restenosis occurs to a degree that calls for a further procedure within six months in about 20% of patients: repeat angioplasty may be performed with a similar risk of restenosis.

The total need for angioplasty in the United Kingdom is hard to define, partly because the indications for the procedure are evolving. It should be seen as complementary to coronary artery bypass grafting (CABG) and not only as an alternative form of therapy. In most western European countries the number of angioplasties is at least 50% of the number of CABG operations; this indicates an immediate need for 300 angioplasties per million of the population in the United Kingdom. With constraints imposed by limited funding and a shortage of trained operators only 127 procedures per million of the population were performed in 1989.[25] Provision of PTCA must be placed on the same formal footing as coronary surgery with a designated budget and planning of facilities. Cardiac centres should have at least two consultant cardiologists or radiologists trained in angioplasty so that acute procedures can be carried out and other doctors trained for the necessary expansion in numbers.

Surgical cover is required unless surgical intervention would be inappropriate. Immediate coronary grafting is required in about 2% of procedures in order to deal with acute occlusion of large coronary arteries. The time within which an operating theatre should be available will vary with the nature of the case. Surgical cover should normally be provided by an operating theatre in the same building and future developments should be planned on this basis. It may be feasible, however, as an interim measure, to use another building or nearby hospital if rapid transfer can be achieved. Arrangements for cardiac surgery inevitably take a short time and transfer should not be a limiting factor that puts the patient at further risk.

SPECIALISED ARRHYTHMIA SERVICES

6.5 Though rhythm disorders may require no treatment or only simple treatment, many call for special expertise for assessment and management. The scope for the successful relief of symptoms or for improvement in prognosis in patients with refractory or dangerous arrhythmias has widened since the publication of the third joint colleges report. Arrhythmology has developed as an important subspecialty of cardiology, calling for skills in electrophysiology, special purpose pacemakers, catheter ablation of elements of the conducting system, and the use of implantable defibrillators. The arrhythmologist must also work closely with surgeons who have a similar specialised interest because the preferred treatment for some patients will be surgical, and both physicians and surgeons must be involved with implantation of defibrillators. These activities are complex, requiring the use of specialised equipment and the support of trained technical staff, and are justified by the striking results. The commitment required for the provision of a specialised arrhythmia service should not be underestimated because investigation is time consuming and can be accommodated only where facilities for catheterisation are adequate. In terms of surgery, we believe that up to 30 operations per million population per annum is a reasonable estimate for the next decade and that present planning of centres should be made on this basis. Whether this figure proves to be appropriate depends on the assessment of the merits of surgical and other methods as the subspeciality develops.

The committee recommends that every effort be made to make these new and successful treatments more widely available.

X RAY SAFETY FOR CARDIAC PROCEDURES

6.6 The development of coronary angioplasty has re-emphasised the importance of effective radiation protection. The *Ionising Radiations Regulations 1985* cover the safety standards for the protection of public and workers. They state the dose limits and include the requirements for monitoring radiation and the appointment of medical physicists who are trained as radiation protection advisers and supervisors. Each employer (that is, the health authority) has a statutory duty to ensure compliance with the regulations. In practice the responsibility usually lies with the district general manager; radiation protection advisers must be employed both to advise on regulations and to review protective measures within hospitals. The health authority is required to appoint, in writing, one or more advisors as radiation protection supervisors to ensure that work is carried out in accordance with the regulations.

Staff working with *x* rays must be monitored to ensure that their doses are as low as reasonably practicable, particularly as the statutory dose limits are under constant review. Doses to patients need to be monitored periodically to ensure that they are also as low as practical and are within the guidelines of the *Ionising Radiation (protection of persons undergoing medical examination or treatment) Regulations 1988*. Protection measures required in hospitals include the provision of adequate shielding. Consequently any plans for new developments should be discussed with the radiation protection adviser at an early stage.

7 Supra-regional specialties

A supra-regional speciality is defined as a clinical activity of such complexity or limited application that the service itself cannot justifiably be provided by every region in the country. The Department of Health has agreed to provide top slice funding for a maximum of nine supra-regional units in any given discipline. Because there are fifteen health regions in England and Wales it is thought that if the figure of nine is exceeded then the clinical service involved should rightly become a regional responsibility and not receive preferential funding.

TRANSPLANTATION

7.1 A steady growth in transplantation surgery has occurred since the time of the last joint college report: the number of units recognised and funded supra-regionally for this work has increased. A balance needs to be struck between the aspirations of units not currently undertaking transplantation that wish to do so, the supra-regional funding concept, and the supply of donor organs.

To date, the controlled development of heart and heart/lung transplantation in designated centres has been successful and, although it may be desirable to see transplantation develop into a regional responsibility, for the time being it would seem reasonable to continue to limit the number of centres.

NEONATAL AND INFANT CARDIAC SURGERY

7.2 It is important that the supra-regional concept should continue to apply to units concerned with surgery for congenital heart disease in infants and neonates. Periodic review of units undertaking this type of work is necessary to ensure that designation is appropriate and that both the volume and standard of work being carried out justifies continued supra-regional funding.

8 Paediatric cardiology

8.1 Since the 1979 report of the British Paediatric Association Working Party on Cardiac Services for Children in England and Wales[26] and the two reports of the Joint Cardiology Committee of the Royal College of Physicians and Surgeons,[1 27] the sub-specialty of paediatric cardiology has changed and expanded considerably. As a result of a crisis in staffing in paediatric cardiological units in 1987 (two new consultant posts and two existing posts at that time were not filled because of lack of suitably trained applicants), the Royal College of Physicians and the British Cardiac Society set up a Joint Working Party to examine the causes of the problem and to make recommendations for the future. This working party has completed a report on which the following paragraphs are based.[28] Recognising that some of the problems lay in the training of doctors for consultant posts, a new schedule of training was constructed.

8.2 Ten new posts and a further 11 replacement appointments due to retirement or resignation will have to be made by the end of the century. The existing shortfall will continue because the six existing senior registrar positions are unlikely to cope with the necessary replacements. There is no way to solve the immediate problem by planning, but health authorities should be encouraged to make proleptic appointments and to send suitable candidates to complete their training before taking up full-time employment.

8.3 Since 1980 the specialty has expanded to 48 full-time consultants and diversified in its activities. Prenatal cardiology is now part of the work of a paediatric cardiologist; only the practising paediatric cardiologist is able to advise the obstetrician and the parents of the unborn child as to prognosis for the fetus with congenital heart disease. The new technique of fetal echocardiography is difficult and very time consuming.

8.4 Cardiac catheterisation of congenital heart disease was expected to diminish with the advent of sophisticated non-invasive techniques such as cardiac ultrasound and magnetic resonance imaging. Although many congenital malformations are now treated medically or surgically without invasive investigation, the amount of catheterisation has not fallen—indeed, it has increased. This is undoubtedly owing to a rise in the number of interventional procedures including angioplasty; balloon dilatation of valves; transluminal plugging of ducts, collateral arteries, and shunts; and more recently the closure of septal defects.

8.5 With the centralisation of congenital heart disease management in regional centres, affected children may have to travel long distances for their follow up and treatment. Paediatric cardiologists in supra-regional centres attend peripheral clinics throughout their catchment areas on at least one day a week.

8.6 All existing mainland centres whether offically designated supra-regional or regional that offer paediatric cardiological services serve a minimum population of three million people. Some of the larger centres serve very large populations of five to six million. The committee recommends that one consultant paediatric cardiologist per million of the population should be aimed for in the near future. This in effect means that no unit will have less than three consultants, very much in line with the general recommendations of the Department of Health for more junior grades, and particularly important in a consultant orientated specialty. This recommendation would result in the number of consultants in the United Kingdom rising from 48 to about 60 to cope with the present and future workload. This increase cannot be filled from existing senior registrar posts and the committee recommends that every supra-regional centre should have a senior registrar training post—an increase of between three and five such positions.

8.7 Improvements in surgical and medical treatment of congenital heart disease have resulted in considerable numbers of patients surviving into adolescence and adult life. Many require special management throughout the remainder of their life and supervision of some lesions may be required for 50–60 years. Patients must be treated by cardiologists trained in the appropriate techniques and appointed to strategic centres throughout the country. A solution would be to train adult cardiologists in congenital heart disease and, in association with paediatric cardiologists, to set up supra-regional centres for the ultimate management linked to regional care (supervision) clinics, as has been established for paediatric cardiology.

8 Adolescent/adult congenital heart disease

9.1 Probably 60–70% of patients treated for congenital heart disease in infancy and childhood reach adult life. The experience at the National Heart Hospital, which has provided special facilities for treating adolescents and adults with congenital heart disease since 1976, shows a change in the reasons for admission and increasing age of patients. In the past four years the inpatient requirements of patients aged 20–30 years have exceeded those of the adolescents, as did those of the over 30s in 1989. Patients with more complex malformations are now surviving beyond childhood to present difficult problems for the cardiologist. Acquired coronary artery disease and hypertension are beginning to present problems added to those of the underlying congenital heart disease. Approximately 50–60% of long term survivors have a problem that requires cardiac and/or cardiac surgical advice and treatment. There are increasing cardiac surgical requirements for congenital heart disease with the expanding need for reoperation of the first definitive repair. The need for such reoperations continues to the fourth decade and provision will be required for the long term survivors who require surgery for acquired coronary artery disease.

9.2 Increasing outpatient consultations related to the underlying heart disease are needed for advice on topics such as contraception and pregnancy, employment, insurance, driving licences, extracardiac surgery, psychosocial problems, housing, and even prison sentences and necessitate a structured organisation. An integrated fetal scanning service is necessary since this group has a higher than normal risk of fetal abnormality.

9.3 The optimal care of these patients, particularly those with complex disease, should be centralised in four or five centres with the specialised technology and necessary cardiological and cardiac surgical skills. The main demands, besides adult inpatient facilities, are for diagnostic magnetic resonance imaging; echocardiography (including transoesophageal echocardiography); arrhythmia and failure management; and properly timed investigation, intervention, and reoperation. At the moment relatively few doctors have the experience and skills to provide care throughout this wide age range in what is a new and changing clinical practice. Attention must be directed to the provision of appropriately trained clinicians. In the immediate future the staffing of departments that provide care for adults with congenital heart disease will vary; some will have adult cardiologists specifically trained in the subject while others will rely heavily on paediatric cardiologists who continue the care of their patients into adult life, frequently with the cooperation of an adult cardiologist. The important issue is the delivery of high quality care to the patient rather than the exact designation of those involved.

9.4 Arrangements for the care of these patients must be flexible and integrated. Some paediatric cardiologists have the training and interest but no beds or facilities or adequate training in management of acquired degenerative cardiovascular diseases. The involvement of paediatric cardiologists will be essential during the period of establishing optimum centralised care. Most patients are referred to local cardiologists, but ultimately care should be by specially trained cardiologists in appropriately equipped centres. Those requiring further surgery or with complex lesions needing particular advice should have the opportunity of reaching supra-regional centres, which will require supra-regional funding.

10 Cardiac services for the elderly

10.1 By the year 2020 it is expected that one in five of the population will be at least 65 years old. Age alone should not exclude patients from potentially useful treatment. The value of coronary thrombolysis, pacing, and coronary angioplasty are well established in this age group. The use of cardiac surgery, with the exception of transplantation, has also increased in older patients. Changing demography and developments in cardiology will need to be considered in planning services for the future.[29]

11 Cardiac rehabilitation

11.1 Rehabilitation after myocardial infarction or coronary artery surgery is widely practised in North America, Europe, and Australia. After programmes began in the early 1970s the development of cardiac rehabilitation in Great Britain and Ireland has been slow, but a growing number of programmes have been established in the past five years. Nevertheless, a survey carried out in 1989 by the Coronary Prevention Group showed that of the 210 health districts in England and Wales only 119 had cardiac rehabilitation programmes. Of these only 61 were supervised by a consultant and only 27 by a cardiologist.

11.2 The physical and psychological effects of myocardial infarction or cardiac surgery are particularly evident in those in whom the disease strikes without warning. Proper counselling by doctors in hospital or by their general practitioners on discharge may do much to allay anxiety and encourage the return to normal activities. Cardiac rehabilitation facilitates this process, both by supervised exercise and by group therapy in meeting with other patients, so that confidence is restored much more quickly. Many studies have shown improved exercise capacity and a quicker return to work in those who have participated in a formal exercise programme than in those who have not.

11.3 In the British Isles, cardiac rehabilitation programmes have a fairly uniform structure with courses beginning two to six weeks after the event and continuing for four to 12 weeks. The usual pattern is graded exercise with some circuit training once or twice a week, supervised by physiotherapists and a nurse or doctor, and with some monitoring of pulse or blood pressure. Spouses are encouraged to attend and there is generally an opportunity for discussion with the dietitian, social worker, or psychologist who attends the sessions.

11.4 The reticence of cardiologists in the United Kingdom to become involved in cardiac rehabilitation is probably attributable to two issues. First, does cardiac rehabilitation do anything to improve prognosis in the long term? The answer to this has always been equivocal because of patient selection and the different types of programme undertaken in different countries. Two recently published meta-analyses, however, do suggest a 20% improvement in prognosis in those who participate in cardiac rehabilitation compared with those who do not.

Secondly, there has been concern about safety. Exercising the patient before the myocardial infarct has fully healed may seem risky, but in practice the incidence of serious or fatal events is very small, probably of the order of one in 100 000 patient attendances. This is probably not very different to the event rate that occurs anyway in the early phases of recovery from myocardial infarction.

11.5 Cardiac rehabilitation should be a service available throughout the country but at present little more than half of patients have access to such facilities. Rehabilitation programmes are not expensive. Although supervision could be undertaken by any physician with the interest and aptitude, a cardiologist would be the most appropriate in that he can best coordinate rehabilitation with exercise testing and the need to assess the patient formally for angiography. A crucial aspect of rehabilitation is the appointment of one person (usually a nurse or physiotherapist) with special responsibility for the programme.

12 Training

12.1 The training programmes for cardiology must take account of the range of skills that are now required—from an interventional cardiologist in a major centre to the cardiovascular physician in a district hospital who may take some responsibility for general medicine. The core of training should be similar. All trainees should acquire expertise in congenital heart disease; knowledge of new developments in cardiac care that include interventional procedures, experience in catheterisation, and coronary angiography; skill in arrhythmia control, pacing techniques, echocardiography, and Doppler; and a sound knowledge of the non-invasive tests undertaken by physiological measurement technicians. They must also take an interest in epidemiology, prevention, resuscitation, and rehabilitation.

12.2 Training in cardiology has always been onerous, but it has become more so with the technological advances of recent decades. Both instruction and experience are necessary, and training must be spread over several years if reasonable confidence is to be attained in the relevant fields within the specialty. At the same time due regard must be paid to a broad knowledge of general medicine. The current recommendations are for a total of at least five years training in cardiology after general professional training plus a year at senior registrar level in general medicine. In addition, those interested in following a career in interventional cardiology would usually require an extra year to acquire the necessary skills and experience. Cardiologists with an academic interest may well want to spend one or two years in research in addition to the basic requirements for a service commitment. The recommendations are in line with those of the European Community.

12.3 The current recommendations of the Joint Committee on Higher Medical Training for training in paediatric cardiology suggest a flexible programme, normally occupying four years. At least two years should be in a specialist paediatric cardiology centre providing all of the experience that is associated with the supraregional centres. It is recommended that either during general professional or higher specialist training, 6–12 months should have been spent in adult cardiology and 1–2 years in paediatrics, including six months in a regional neonate unit. A revision of these recommendations has been considered by a Paediatric Cardiology Working Party in order to relate them more closely to those for adult cardiology. The normal training period would then be increased to occupy six years, three at Registrar level and a further three at Senior Registrar level. Ideally one of these years should be spent in research. These recommendations are still under discussion.

13 Academic cardiology and research

13.1 Research has an important part to play in providing quality in medical services. Increasingly, it is being appreciated that the scientific assessment of treatments (as by clinical trials) and medical audit are essential components in the advance of clinical practice. Over and above this, a research experience is a valuable element in the training of physicians, and it is essential that both basic and clinical research of excellence is carried out in British cardiac centres. It has become progressively more difficult to provide opportunities for those who wish to train in research, both because of the lack of career posts in the basic sciences and because the number of honorary posts for clinical research workers is in danger of being severely limited by the quotas determined by the Joint Planning Advisory Committee. The role of research must be taken into account by those planning cardiac services and by those concerned with training.

14 Audit

14.1 At its simplest, medical audit involves peer review of a department or hospital that should encompass all clinical activities including the inpatient and outpatient and diagnostic services, and the operating department. It will review waiting list times as an indirect indication of provision and outpatient waiting times as an index of one aspect of quality of service. It should permit comparisons between hospitals and regions and also differences in national provision.

14.2 National registries on pacemaker implantation and percutaneous cardiac interventional procedures already exist: the British Pacing and Electrophysiology Group has agreed upon guidelines for peripheral pacing clinics, and the Society of Thoracic and Cardiovascular Surgeons has since 1977 published an annual report of cardiac surgical procedures carried out in the United Kingdom.

14.3 A committee, drawn from members of the Cardiology Committee of the Royal College of Physicians and the Council of the British Cardiac Society has been established to initiate and facilitate audit in the specialty. Current projects include audits of the management of acute myocardial infarction, complications from cardiac catheterisation, and proposals for audit of cardiac units in district general hospitals.

14.4 All cardiac departments should cooperate with the audit activities of other specialties in their hospitals, hold regular audit meetings, and maintain appropriate records.

14.5 As with many developments in patient care audit has resource implications with respect both to funding and the availability of clinicians' time. The national registries will be of greatest importance in identifying levels of provision, or its lack, and require to be properly supported.

1 Royal College of Physicians of London and the Royal College of Surgeons of England. Provision of services for the diagnosis and treatment of heart disease in England and Wales. Third Report of the Joint Cardiology Committee. *Br Heart J* 1985;53:477–82.

2 Office of Population Census and Surveys. *Mortality Statistics Series DH1 No 17 Table 24*. London: HMSO, 1987.

3 Office of Population Census and Surveys. *Deaths by Cause 1988 registrations Office of Population Census and Surveys monitor DH2 89/2*. London: HMSO, 1989.

4 Catford JC, Dillon A, Maryon-Davis A, Morris J, Rose GA, Tudor Hart J, *et al*. Coronary Heart Disease Prevention, Action in the UK 1984–1987, National Forum for Coronary Heart Disease Prevention, Health Education Authority. London: 1988.

5 Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;51:595–605.

6 Shaper AG, Cook DG, Walker M, Macfarlane PW. Recall of diagnosis by men with ischaemic heart disease. *Br Heart J* 1984;51:606–11.

7 Welsh Heart Programme Directorate. *Heart of Wales: clinical results of the Welsh Heart Health Survey 1985. Heartbeat Report No 20*. Cardiff: Heartbeat Wales, 1987.

8 Office of Population Census and Surveys. *Hospital inpatient enquiry*. HMSO: London, 1986.

9 Sutton GC. Epidemiologic aspects of heart failure. *Am Heart J* 1990;120:1538–40.

10 Somerville J. Congenital heart disease in the adolescent. *Arch Dis Child* 1989;64:771–3.

11 World Health Organisation European Collaborative Group. European collaborative trail of multifactorial prevention of coronary heart disease: final report of the six year results. *Lancet* 1986;19:869–72.

12 British Cardiac Society Working Group. Report on Coronary Disease Prevention, London, British Cardiac Society. London: 1987.

13 King's Fund. *Consensus statement on blood cholesterol measurement in the prevention of coronary heart disease*. London: King's Fund, 1989.

14 Department of Health. *Working for patients*. London: HMSO, 1989.

15 Department of Health. *The GP contract*. London: HMSO, 1989.

16 MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke, and coronary heart disease. *Lancet* 1990;335:765–74.

17 Kannel WB. Update on the role of cigarette smoking in coronary artery disease. *Am Heart J* 1981;101:319–28.

18 Adgey AAJ, Devlin JE, Webb SW, Mulholland HC. Initiation of ventricular fibrillation outside hospital in patients with acute ischaemic heart disease. *Br Heart J* 1982;47:55–61.

19 Jaggarao NSV, Sless H, Grainger R, Vincent R, Chamberlain DA. Defibrillation at a football stadium: an experiment with Brighton and Hove Albion. *BMJ* 1982;284:1451.

20 Cobbe SM, Redmond MJ, Hollingworth J, Carrington DJ. Heartstart Scotland: initial experience of a nationwide scheme for out of hospital defibrillation by ambulance crews [abstract]. *Br Heart J* 1990;65:65.

21 Marsden AK, Chamberlain DA. Guidelines for cardiopulmonary resuscitation. *BMJ* 1989;299:442–8.

22 Report of a working group of the British Cardiac Society. Cardiology in the district hospital. *Br Heart J* 1987; 58:537–46.

23 Chamberlain D, Bailey L, Sowton E, Ballantyne D, Boyle DMcC, Oliver M. Staffing in cardiology in the United Kingdom 1988. Fifth biennial survey. *Br Heart J* 1989; 62:482–7.

24 MacRae CA, Keywood C, Marber MS, Joy M. The need for invasive cardiological assessment and intervention: a ten year review. *Br Heart J* 1991 (in press).

25 Hubner PJB on behalf of the British Cardiovascular Intervention Society. Cardiac interventional procedures in the United Kingdom in 1989. *Br Heart J* 1991;66: 467–71.

26 Gray OP, Mann TP, Simpkiss MJ, Joseph MC, Jones RS, Watson GH. Cardiac services for children in England and Wales. Report of a Working Party of the British Paediatric Association and the British Paediatric Cardiology Section. February 1979.

27 Second Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England on combined cardiac centres for investigation and treatment with a note on the requirements of cardiology in hospitals outside such a centre. *Br Heart J* 1980;43:211–9.

28 Report of a joint working party of the British Cardiac Society and the Royal College of Physicians of London. The future of paediatric cardiology in the United Kingdom. *Br Heart J* 1991 (in press).

29 Royal College of Physicians. Report of the Joint Working Group on cardiological interventions in elderly patients. *J R Coll Physicians Lond* 1991;25:197–205.

PLANTS IN CARDIOLOGY

Cardiac glycosides

Foxglove, *Digitalis purpurea* (Scrophulariaceae), was a traditional English folk remedy for dropsy (right heart failure) and its use by an old woman in Shropshire and a carpenter in Oxford led Dr William Withering to undertake his fine scientific study of it from 1775 to 1785. But in spite of his advocacy, its use in dropsy lapsed in the next 100 years though it was used in other diseases such as delirium tremens, epilepsy, and tuberculosis.

Nerium oleander L.
Gerard J. *The Herball.*
London: 1633.

By contrast with its neglect in dropsy, its effect on the heart beat gained emphasis. J-B Bouillaud lauded it in 1835 as "le véritable opium du coeur" and gave it by blistering the precordium and covering the area with powdered digitalis. By 1873 F T Roberts had found that digitalis relieved the pulmonary symptoms of mitral disease "especially when there is great irregularity of the heart". However, it was the work of James Mackenzie, a general practitioner in Lancashire that gave digitalis its established position in the treatment of heart failure. His 10 year analysis of the venous pulse in 500 patients led him in 1902 to identify the arrhythmia later shown to be atrial fibrillation and to show that digitalis was of particular value when ". . . . heart failure was due to the excessive rate of the ventricle, the ventricle being exhausted for want of rest . . . the effect of the drug was at times phenomenal". He recognised what Withering had not—that the relief of dropsy was directly due to the action of the heart.

A cardiac glycoside was first isolated in 1875 when digitoxin was prepared from *D purpurea.* Soon afterwards ouabain and strophantin-K were isolated from the African trees *Acokanthera* and *Strophanthus* which were used as arrow poisons. American pioneers learnt from the Indians that *Apocynum,* dogbane, was a diuretic and it became known as the vegetable lancet because it worked as well as venesection. These three genera belong to the family Apocynaceae which has six other members containing glycosides and also includes the genera yielding resperine and the vinca alkaloids. Altogether in twelve plant families there are 37 genera with glycosides. One of these is the plant used longest as a diuretic, *Drimia maritima* (squill), which is mentioned in the Ebers papyrus of 1500 BC.

I sometimes wonder whether the eminence of digitalis has inhibited a thorough evaluation of the other glycosides such as the powerful oleandrin found in *Nerium oleander* (*British Heart Journal* 1985;54:258–61).

A HOLLMAN

Br Heart J 1992;67:117

BRITISH CARDIAC SOCIETY NEWSLETTER

We start this newsletter with the sadness of saying farewell to Dennis Krikler as editor of the *British Heart Journal*. There are many tributes to him in this issue, but we are very anxious to add our own words of thanks to Dennis who has been a very good friend and we owe him a great debt, and he will know that the continuing excellence of the journal is an enduring tribute to his work. It should also be noted in this column that it was Dennis who had the happy idea of a monthly newsletter from the British Cardiac Society, and we believe this provides a valuable service.

Plans are now well advanced for the society to acquire its own offices. Agreement has been reached to acquire a Georgian office building on the east side of Fitzroy Square, W1. The appropriate legal process is underway and the purchase should be completed by late November.* The society, which is buying the freehold of the property, has been advised by two international property consultants.

Fitzroy Square is situated about 400 metres from the Royal College of Physicians, just south of Euston Road and close to Warren Street and Great Portland Street tube stations. The square is pleasant and partly pedestrianised. The building has a total floor area of approximately 4000 square feet with four floors and a basement. It was refurbished three years ago and many period features are present throughout the building. The society will be moving into the new offices early in 1992. Although we are sorry to be leaving the facilities of the Royal College of Physicians, we are not moving very far away and our close links will continue.

The new premises will provide the society with good office accommodation and the ability to host small meetings. It is hoped to accommodate the editorial offices of the *British Heart Journal* in the building. It will also provide the society with an opportunity to offer increased support to affiliated groups. Initially there will be spare office facilities which we propose to offer to a friendly medical society. It is comforting for the society to have a substantial permanent home.

This month we have contributions to our newsletter from several of our members. This is a society newsletter, and we welcome its use by those who have relevant information they wish to pass on.

Keith Fox has written with two items: first, medico-legal representation and secondly, information on the British Society for Cardiovascular Research.

"The ethical and legal committee of the British Cardiac Society proposed that members of the Society who are willing to serve on the specialist medico-legal panel of the society should submit their names and the outline of the area of their expertise so that a list of such individuals could be compiled for the law societies of England and Wales and Scotland. Clearly, no obligation is implied and there is no question of exclusivity. The legal profession would be free to seek specialist advice, whether or not such an individual had volunteered to serve on the panel.

We are pleased to see that, so far, 85 cardiologists have put forward their names for inclusion in this list and we believe that this will permit a more comprehensive and representative basis for seeking specialist cardiac opinion. If any further members wish to be included on the medico-legal panel, further forms are available from the Secretary of the British Cardiac Society. Clearly, the ethical and legal committee does not think that it is appropriate for the committee to determine or monitor the areas, or indeed the degree, of specialist expertise of individual members. Furthermore, a member would be free to withdraw from the advisory panel at any time. The corollary is that opinions expressed by individual members of the panel cannot necessarily be interpreted as representing the views of the committee or the society.

In response to a proposal from the British Society for Cardiovascular Research, the council of the British Cardiac Society has agreed to support a lectureship at each of the biannual meetings of the British Society for Cardiovascular Research. In return, the British Society for Cardiovascular Research would allow members of the British Cardiac Society to attend these meetings without payment of the registration fees. Information about the biannual meetings is included in the mailing from the British Cardiac Society.

After the introduction of only one annual meeting of the British Cardiac Society, concern has been expressed that there may be insufficient opportunity for younger investigators to participate in academic meeting at which original material is presented and discussed. The proposals allow just such participation in meetings at which high quality basic and applied cardiovascular research material is presented. The meetings of the British Society for Cardiovascular Research and the workshops have been well attended and have provoked active discussion. We would like to draw your attention to the opportunities presented to participate in and to submit material for presentation to the meetings."

Peter Hubner passess on a suggestion for a practice that has worked well in his area. The Leicester cardiologists have produced small stickers that are sent to the general practitioners of patients with valvar or congenital heart disease. The stickers can be put on the patient's folder. They state only: "Endocarditis alert! Blood cultures before antibiotics for unexplained fever". Its simple, easy, and cheap. It may also save a lot of anguish in some instances. We ourselves believe that in time, we would have had the same idea...

John Goodwin, Chairman of the National Forum for Coronary Heart Disease Prevention writes: "Readers of the newsletter may like to have up to date news about the forum which was set up (as the National Co-ordinating Committee) after the Canterbury conference in 1983 with the title Action to prevent Coronary Heart Disease. The purpose of the forum is to co-ordinate and facilitate the activities of organisations and individuals concerned with all aspects of coronary heart disease prevention. It has over 30 member organisations including the British Cardiac Society, the British Heart Foundation, the Coronary Prevention Group, Action on Smoking and Health, the Coronary Artery Disease Research Organisation (CORDA), the Chest, Heart and Stroke Association, and the British Medical Association. The Royal Colleges are fully represented, as are nursing, pharmaceutical, dietetic, primary health care organisations; the Health Education Authority; the Health Promotion Authority for Wales; the Health Education Board for Scotland; and the Health Promotion Agency of Northern Ireland. Non-medical organisations, such as the Sports Council and the Trades Union Congress are also members.

Each organisation sends a representative to the biannual forum meeting. In addition to co-ordinating the activities of its members, the forum (which is independent and free to express the wishes of its membership) responds to their initiatives and suggestions, identifies areas of agreement and controversy, and surveys the need for action. The forum advises the Health Education Authority's Look After Your Heart programme, government, and industry. In addition to the core activities, the forum undertakes special projects such as workshops, as agreed by the membership and the executive committee. So far, these have included projects on school meals, undergraduate medical education in coronary heart disease prevention (in which the British Cardiac Society and the British Heart Foundation took leading roles), cardiovascular health in the workplace, and coronary heart disease in women. Appropriate member organisations were heavily involved in their planning and execution.

Interest and awareness of coronary heart disease prevention is steadily increasing among general practitioners and primary health care workers in all fields. So far cardiologists have not always been noted for their interest. This is understandable because of their heavy load of clinical and research responsibilities. But it is vital that they fulfil their role, including secondary prevention. Further information can be requested and suggestions sent to the Forum's Co-ordinator, Ms Imogen Sharp, MSc, National Forum for Coronary Heart Disease Prevention, Hamilton House, Mabledon Place, London WC1 H9TX (tel: 071 383 7638)."

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
1 St Andrew's Place,
London NW1 4LB

**Please note, we have completed our move. Our new address is 9 Fitzroy Square, London W1P 5AH. Telephone: 071 383 3887; Fax: 071 388 0903.*

NOTICE

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts was 3 January.

Br Heart J 1992;67:118–9

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

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Three complete sets of the manuscript (with 3 sets of figures) are submitted (this also applies to amended versions). ☐

The manuscript is typed double spaced throughout on one side only on A4 opaque white bond paper with wide margins all around. ☐

The manuscript is arranged as follows: (1) title page, (2) abstract, (3) text, (4) references, (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1. ☐

The last name of the first author is typed at the top right corner of each page. ☐

A covering letter is signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. ☐

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The title and authors' names are typed on the title page. ☐

Case reports have only three authors. ☐

The address(es) of the institutions from which the work originated with the authors' names are listed underneath. (If there is more than one address several authors' names can be grouped under each appropriate address; strict order of authors' names is not necessary here.) ☐

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Abbreviations other than standard SI units of measurement are not used. ☐

Text

Appropriate headings and subheadings are provided. ☐

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Acknowledgments and details of support in the form of grants, equipment, or drugs are typed at the end of the text, before references. ☐

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References are identified in the text by arabic numerals; no more than three references are cited for any one statement. ☐

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Journal references contain *inclusive* page numbers; book references contain *specific* page numbers. ☐

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31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984;52:304–8.

Chapter in book:

28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1968:134–9.

Book (personal author or authors): (all book references should have specific page numbers)

36 Feigenbaum H. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981:549–63.

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Measurements are given in SI units. ☐

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Statistics

If the same variable is measured by two different methods the agreement between the methods has been assessed according to the guidelines published in the *British Heart Journal* (1988;**60**:177–80). ☐

Statistical measures of variation, such as SD or SEM, are specified and given in parentheses. ☐

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As a service to readers each month the *British Heart Journal* publishes a list of the current contents of *Cardiovascular Research,* a sister journal published by the BMJ Publishing Group in association with the British Cardiac Society.

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Cardiovascular Research is an international journal specialising in all aspects of the cardiovascular system in health and disease. The journal gives priority to studies from the cutting edge of cardiovascular biology. The journal strives to promote links between fundamental research and clinical cardiology and to enhance the understanding of the pathophysiology of cardiovascular disease.

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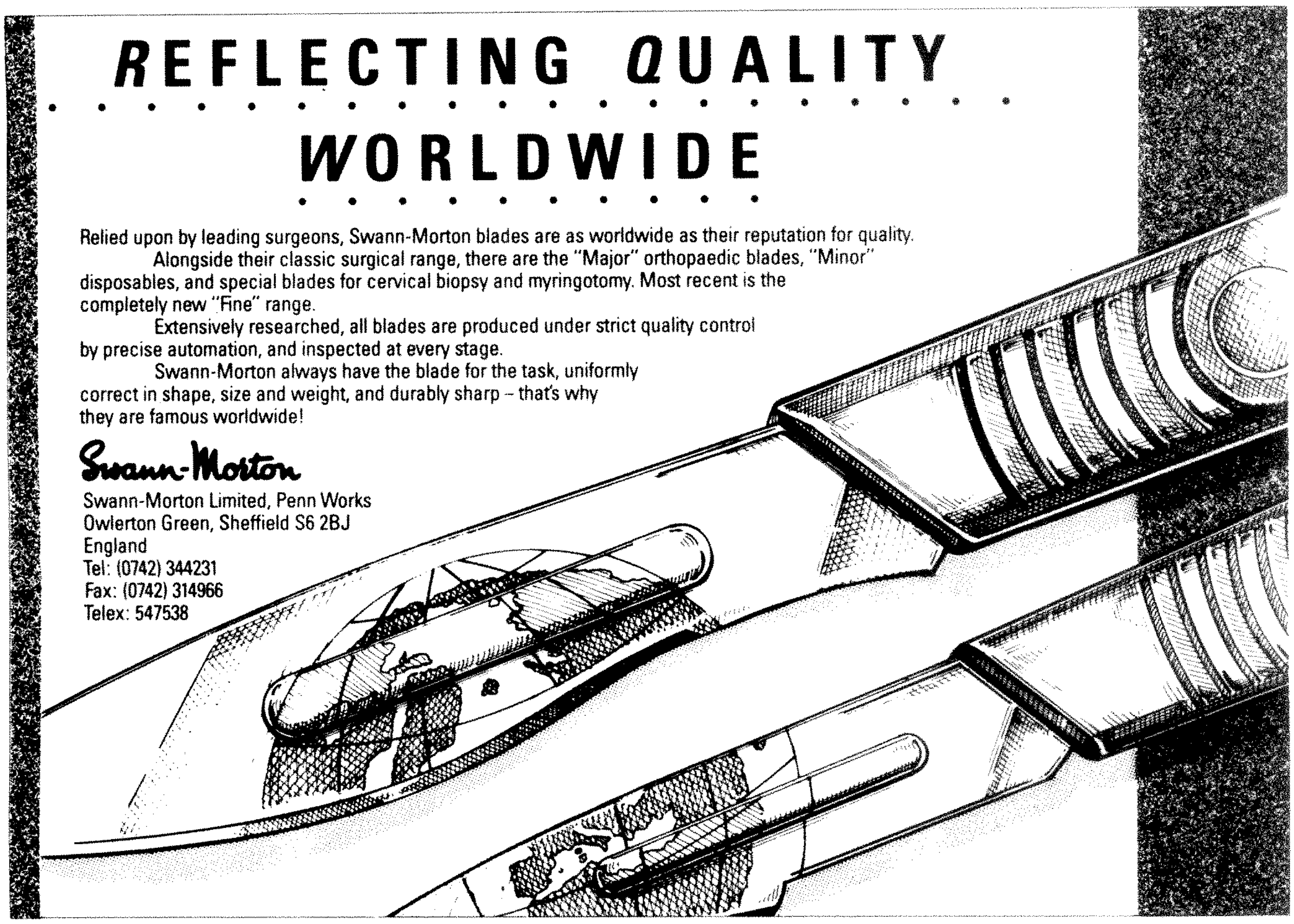

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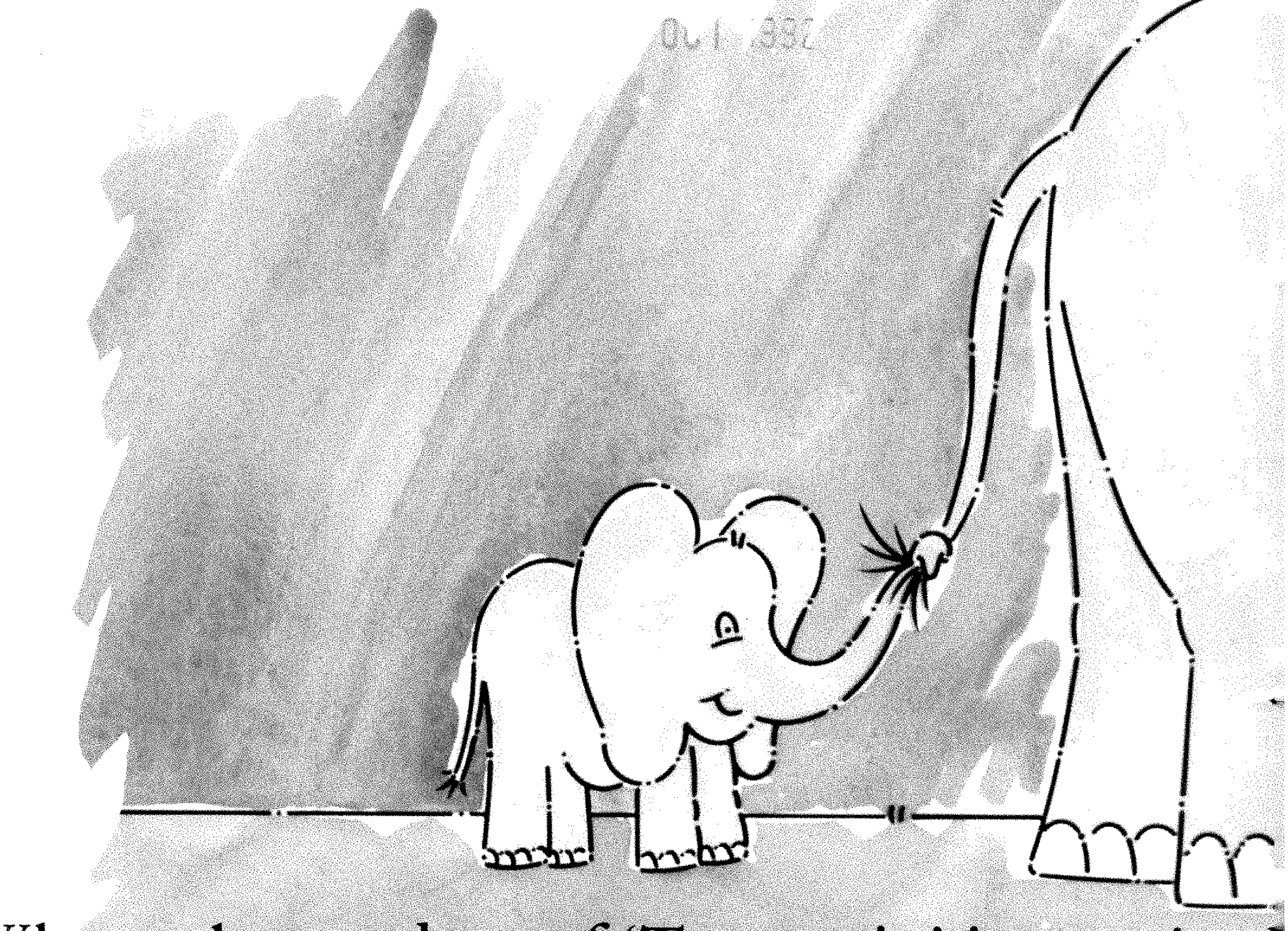

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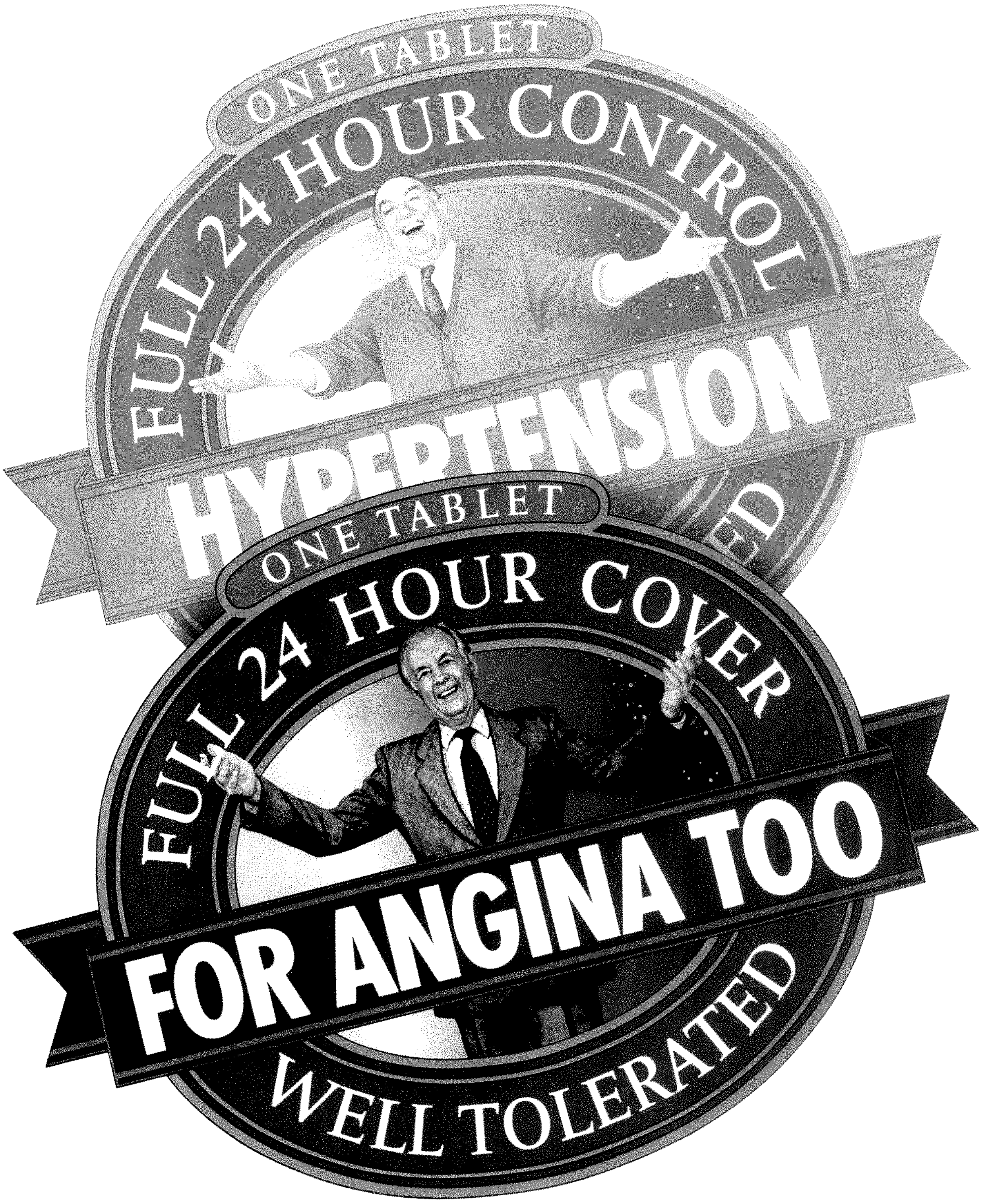

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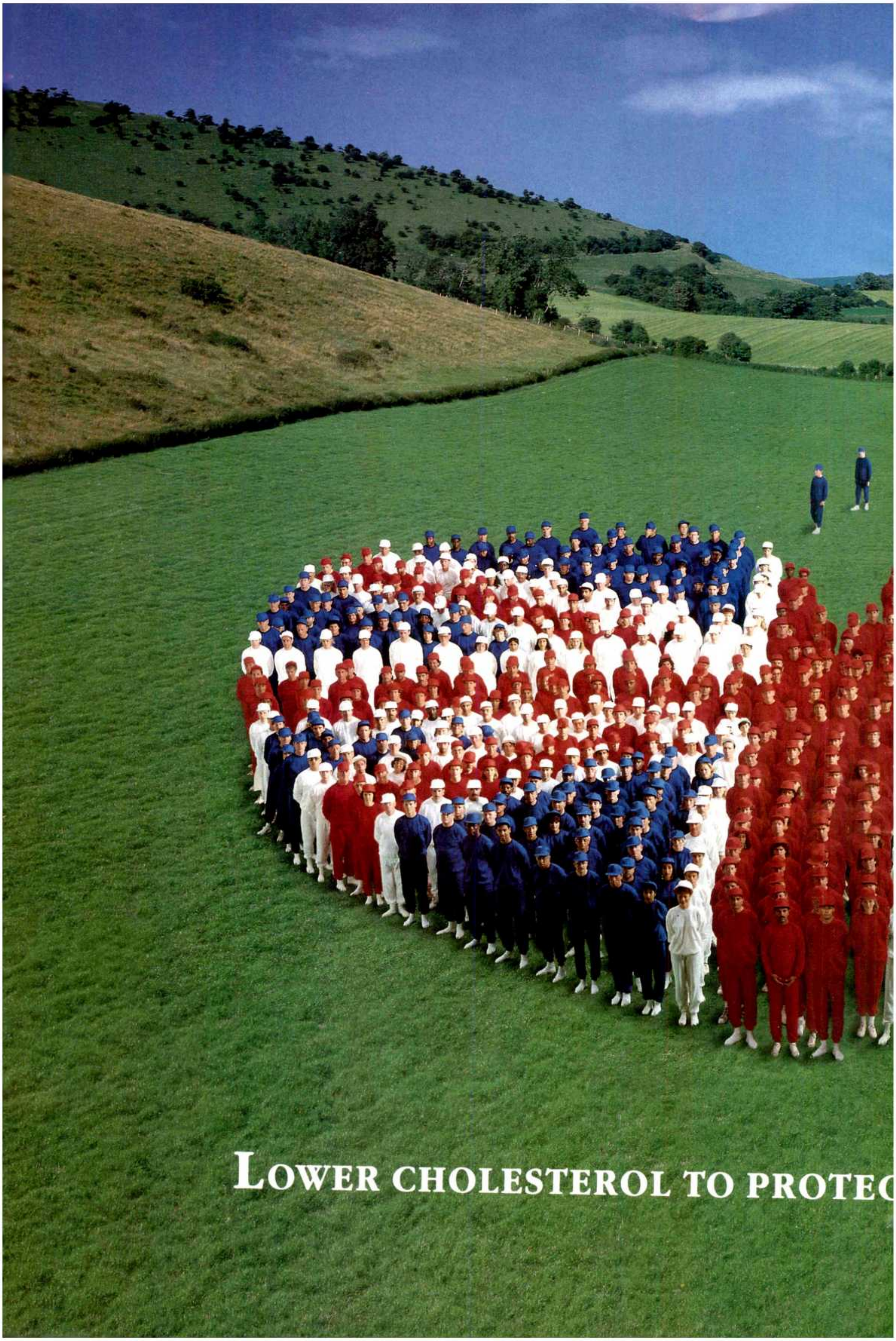

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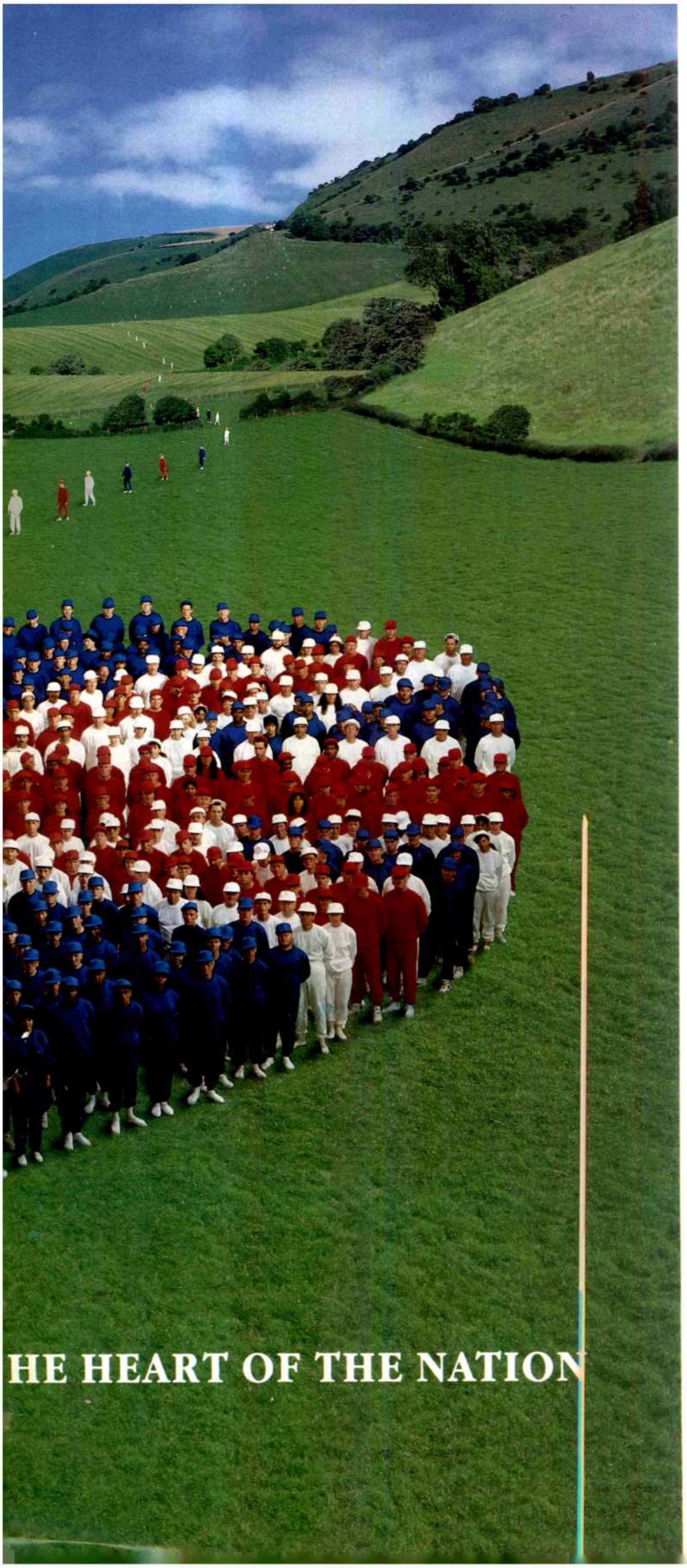
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REFERENCES
1. OPCS Monitor DH2. June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

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Editorial

Single lung transplantation and pulmonary hypertension

There are few successful treatments for pulmonary hypertension. Long-term domiciliary oxygen therapy prolongs survival in patients with secondary pulmonary hypertension resulting from chronic hypoxic lung disease.[1] There is some evidence that the quality of life is also improved.[2] For primary pulmonary hypertension, which is unexplained by cardiac or pulmonary disease, no established medical treatment, other than anticoagulant therapy increases survival.[3] Vasodilatation treatment can improve the quality of life[4] and early evidence from the use of long-term intravenous infusion of prostacyclin in the most severe forms of the disease suggests that survival can be increased.[5]

Heart-lung transplantation has emerged as a successful treatment for a wide range of chronic end stage cardiopulmonary diseases, including pulmonary hypertension.[6] It improves the survival of patients with cystic fibrosis and respiratory failure.[7] In patients with pulmonary hypertension, heart-lung transplantation restores pulmonary vascular resistance to normal.[8] However, the limited availability of donors with both lungs suitable for transplant surgery,[9] impedes the wider use of this treatment. Indeed patients often wait for more than seven months and over a quarter die on the waiting list.

For some diseases, including lung fibrosis and emphysema, the development of single lung transplantation offers certain advantages over heart-lung transplantation.[10] It requires only one suitable lung, which may theoretically increase the supply of donor organs. Because recipients retain their own hearts, they will not experience graft related coronary occlusive disease which limits the long-term success of cardiac transplantation.[11] Actuarial survival after single lung transplantation is approaching that after heart-lung transplantation[9] so it is with special interest we learn of the haemodynamic effects of single lung transplantation on the treatment of pulmonary hypertension. Doig *et al* showed that haemodynamic function improved considerably after single lung transplantation for moderately severe pulmonary hypertension.[12]

This experience encourages the wider use of single lung transplantation perhaps limiting heart-lung transplantation to patients with cystic fibrosis. It also offers the interesting prospect of the use of single lobes of lung for transplant surgery. This has already been described in three cases of childhood pulmonary hypertension by Vaughan Starnes in Stanford, California, and could lead to the use of organs from living donors for lung transplantation. The partial correction of the physiological abnormality would have to be sufficient to justify such a development. The debate on the ethics of live donation has recently been joined[13] and there is an implicit need to balance risks to the donor against the benefits to the recipient. At this early stage when results are very limited, our judgement perhaps should be guarded. However, if the use of single lung transplants grew a further increase in donors would be possible, just as single organ transplants affected the prospects of renal transplantation.[9]

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1 Report of the MRC Working Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;i:681–6.
2 Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". *Lancet* 1981;i:907–9.
3 Dinh-Xuan AT, Higenbottam TW, Scott JP, Wallwork J. Primary pulmonary hypertension: diagnosis, medical and surgical treatment. *Respir Med* 1990;84:189–97.
4 Rich S, Brundage BH. High-dose channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right-ventricular hypertrophy. *Circulation* 1987;76:135–41.
5 Cremona G, Higenbottam TW, Scott JP, Sharples L, Dinh-Xuan AT, Wallwork J. Continuous intravenous infusion of prostacyclin (PGI_2) improves survival in primary pulmonary hypertension [abstract]. *Am Rev Respir Dis* 1991;143:A180.
6 McCarthy PM, Starnes VA, Theodore J, Stinson EB, Oyer PE, Shumway NE. Improved survival after heart-lung transplantation. *J Thorac Cardiovasc Surg* 1990;99:54–60.
7 Sharples LD, Caine N, Hathaway T, Dennis C, Scott JP, Higenbottam TW, Wallwork J. Selection of cystic fibrosis patients for heart-lung transplant and evaluation of improved survival and quality of life [abstract]. *Am Rev Respir Dis* 1991;143:A443.
8 Dawkins KD, Jamieson SW, Hunt SA, *et al.* Long-term results, hemodynamics and complication after combined heart and lung transplantation. *Circulation* 1985;71:919–26.
9 West R. *Organ transplantation.* London: Office of Health Economics. 1991;39–45.
10 Mal H, Andreassion B, Pamela F, *et al.* Unilateral lung transplantation in end-stage pulmonary emphysema. *Am Rev Respir Dis* 1989;140:797–802.
11 Bodek A. Need donor hearts be entirely free from disease? *N Engl J Med* 1989;320:1628.
12 Doig JC, Corris PA, Hilton CJ, Dark JH, Bexton RS. Effect of single lung transplantation on pulmonary hypertension in patients with end stage fibrosing lung disease. *Br Heart J* 1991;66:431–4.
13 Shaw LR, Miller JD, Slutsky AS, *et al.* Ethics of lung transplantation with life donors. *Lancet* 1991;338:678–81.

Br Heart J 1992;67:122–8

ORIGINAL ARTICLES

Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial

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Abstract

Objective—To determine whether concomitant treatment with intravenous heparin affects coronary patency and outcome in patients treated with alteplase thrombolysis for acute myocardial infarction.

Design—Double blind randomised trial.

Treatment regimens—Alteplase 100 mg (not weight adjusted) plus aspirin (250 mg intravenously followed by 75–125 mg on alternate days) plus heparin (5000 units intravenously followed by 1000 units hourly without dose adjustment) was compared with alteplase plus aspirin plus placebo for heparin.

Setting—19 cardiac centres in six European countries.

Subjects—652 patients aged 21–70 years with clinical and electrocardiographic features of infarcting myocardium in whom thrombolytic therapy could be started within six hours of the onset of major symptoms.

Main outcome measure—Angiographic coronary patency 48–120 hours after randomisation.

Results—Coronary patency (TIMI grades 2 or 3) was 83·4% in the heparin group and 74·7% in the group given placebo for heparin. The relative risk of an occluded vessel in the heparin treated group was 0·66 (95% confidence interval 0·47 to 0·93). Mortality was the same in both groups. There were non-significant trends towards a smaller enzymatic infarct size and a higher incidence of bleeding complications in the group treated with heparin.

Conclusions—Concomitant intravenous heparin improves coronary patency in patients with alteplase. Whether this can be translated into improved clinical benefit needs to be to be tested in a larger trial.

The value of thrombolytic therapy in acute myocardial infarction is well established. Alteplase (single chain recombinant human tissue-type plasminogen activator, rt-PA) has been shown to be effective in securing or restoring coronary patency,[1 2] in limiting enzymatic infarct size and preserving left ventricular function,[3] and in improving survival[4] in patients with evolving myocardial infarction. There is limited evidence that alteplase may be more effective than other thrombolytic agents in securing early coronary patency.[5–7]

Most clinical trials so far conducted with alteplase in myocardial infarction have included the immediate co-administration of heparin followed by a maintenance heparin infusion.[1–4 8–10] The rationale for this has been the assumption that patients might be particularly susceptible to early reocclusion in the absence of continuing anticoagulation because alteplase has a short plasma half life and causes relatively little depletion of plasma fibrinogen. Topol and colleagues showed that administration of heparin immediately before the start of a four hour alteplase infusion did not improve patency as assessed by angiography 90 minutes after the start of the infusion.[11] Conversely, the HART (Heparin-Aspirin Reperfusion Trial) investigators,[12] and Bleich and colleagues[13] showed significantly worse patency rates at 18 hours and 48 hours respectively in patients given alteplase plus heparin placebo compared with those given alteplase plus a conventional heparin regimen.

It is important that the present uncertainty over the role of concomitant intravenous heparin with alteplase thrombolysis should be resolved. If heparin is not essential then treatment can be simplified and bleeding complications perhaps reduced. On the other hand if early intravenous heparin is important then the results of the GISSI 2[14] and International Study Group[15] trials comparing alteplase with other thrombolytic agents may be of limited relevance.

We present the results of a randomised, double blind trial designed to compare the effect of immediate intravenous heparin with heparin placebo on coronary patency in patients with clinical and electrocardiographic features of evolving acute myocardial infarction treated with intravenous alteplase plus intravenous or oral aspirin. The trial was also designed to evaluate the incidence of bleeding complications and the effects of heparin treatment on enzymatic infarct size and the prevalence of left ventricular thrombus.

Patients and methods

The trial was conducted in 19 centres in six European countries under the auspices of the European Cooperative Study Group. Centres are listed in the appendix.

ENTRY CRITERIA

Patients aged 21 to 70 years were recruited if they had chest pain typical of myocardial infarction lasting for 30 minutes or longer, if the necessary electrocardiographic criteria were met, and if an infusion of alteplase could be started within six hours of the onset of major symptoms. The electrocardiographic criteria were at least 0·3 mV ST segment elevation measured at 60 ms after the J point in two precordial leads (V1 to V4), and/or 0·2 mV ST elevation in two frontal plane leads or V5 and V6, and/or 0·1 mV ST elevation in two frontal plane leads or V5 and V6 combined with 0·2 mV ST depression in two precordial leads (V1–V4). All patients were required to have given informed consent in a form acceptable to the ethics of medical research committees of the institutions concerned.

EXCLUSION CRITERIA

Patients were excluded if they had had an earlier transmural myocardial infarct less than 14 days before or a previous infarct in a similar location. Patients at increased risk of haemorrhagic complications as defined in previous ECSG studies[3] were also excluded. Cardiogenic shock was not an exclusion criterion.

RANDOMISATION

Patients were registered and randomised by a telephone call to a randomisation centre. Randomisation was blocked by centre, and investigators were instructed to administer a "pack" of medication identified by a code number.

TREATMENT PROTOCOL

Analgesia was given as required. Aspirin was administered as a 250 mg intravenous bolus (continental centres) or as 300 mg orally (United Kingdom centres) followed by 75–125 mg orally on alternate days. Alteplase (Actilyse, Boehringer Ingelheim) was administered intravenously as a 10 mg bolus followed by 50 mg over the first hour and 20 mg over each of the subsequent two hours. The dose was not adjusted for weight. Heparin was administered intravenously as a bolus of 5000 units immediately before the start of the alteplase infusion followed by 1000 units per hour until angiography was performed. Heparin placebo (dilute albumin solution) was prepared in identical vials and given in the same way. Adjustment of the heparin dose according to haemostatic measurements was not permitted.

Guidelines for the correction of haemodynamic abnormalities were specified. Repeated administration of alteplase was permitted in the event of clinical reinfarction, with 50 mg of alteplase if reinfarction occurred within 24 hours or 100 mg if it occurred more than 24 hours after entry.

Heparin was continued after angiography at the discretion of the individual investigator; angioplasty or other necessary intervention was permitted after angiography at the discretion of the operator. Medication at hospital discharge and at follow up was recorded.

ANGIOGRAPHY

Coronary angiography was done 48–120 hours after the start of thrombolytic treatment. At least two projections of the right and three of the left coronary artery were required. Angiograms were recorded on 35 mm cine film and assessed centrally as in previous ECSG studies. Infarct related segments were identified from the angiographic appearances in conjunction with the electrocardiogram recorded before randomisation. Patency was reported in terms of TIMI grades[1] and ECSG stenosis grades.[2]

CARDIAC ENZYME ANALYSIS

Serial blood samples were taken at entry and at 12, 24, 36, 48, 72, and 96 hours. Plasma was separated by centrifugation and the supernatant stored at −20°C before transport on dry ice to a central laboratory. Hydroxybutyrate dehydrogenase (HBDH) activity was estimated in duplicate on each sample and used to calculate cumulative plasma release (Q(24), Q(72)) as a measure of infarct size.[16] The use of enzymatic measurements of infarct size as an outcome measure is subject to potential bias because samples may not be available from patients dying within 72 hours. We therefore imputed "worst case" measurements to these patients.

HAEMATOLOGY

Serial measurements were made of haemoglobin concentration and haematocrit. Blood samples were taken for measurements at a central laboratory of fibrinogen, activated partial thromboplastin time (APTT), and D dimer before treatment was started; at 45 minutes; and at 12, 24, and 26 hours. These measurements were made at a central laboratory and the results will be reported separately.

ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed 48–120 hours after the start of thrombolytic therapy with the aim of identifying left ventricular thrombus. Images were stored on videotape and analysed at a central laboratory by observers who were blind to the treatment allocation.

HAEMORRHAGIC COMPLICATIONS

Haemorrhagic complications were recorded in case record forms according to preset criteria. Major haemorrhagic complications were investigated further by supplementary question-

Table 1 Baseline characteristics for all analysable patients

Characteristic	*Placebo* (*n* = 320)	*Heparin* (*n* = 324)
Age (yr) (range)	56 (26–72)	57 (25–70)
Male (%)	281 (88)	279 (86)
Mean (SD) weight (Kg)	75·28 (12·18)	73·64 (11·14)
Anterior infarct (%)	141 (44)	131 (40)
Previous infarct (%)	17 (5)	20 (6)
History of angina (%)	166 (52)	179 (55)
History of hypertension (%)	84 (26)	76 (24)
Current smoker (%)	201 (63)	200 (62)
Systolic blood pressure (mm Hg) (range)	131 (60–220)	134 (60–220)
Diastolic blood pressure (mm Hg) (range)	84 (50–130)	87 (30–150)
Heart rate per minute (beats/min) (range)	73 (35–120)	74 (34–150)
Haemodynamic state (%):		
Normal	263 (82)	260 (81)
Right heart failure	5 (2)	6 (2)
Mild left heart failure	42 (13)	40 (12)
Overt left heart failure	4 (1)	3 (1)
Shock	6 (2)	14 (4)
Onset symptoms until start infusion (min) (range)	169 (45–392)	170 (32–380)
Randomisation until angiography (h)	83	80

naires and reviewed by a central clinical events committee.

STUDY END POINTS

The main end point of the study was the centrally assessed angiographic patency of the infarct related coronary artery at 48–120 hours. Other outcome measures investigated were (*a*) enzymatic infarct size as estimated by the cumulative release of HBDH into plasma at 72 hours (HBDH-Q72); (*b*) clinical events and bleeding complications up to 48–120 hours angiography and during the whole hospital stay; (*c*) the prevalence of echocardiographically assessed left ventricular thrombus.

TRIAL SIZE AND POWER CALCULATION

Power calculations before the trial started indicated that if a patency rate of 80% at 48–120 hours was assumed for the group receiving alteplase, aspirin, and heparin then a trial size of 440 patients would be required to demonstrate a 14% difference in patency with 80% power at the p = 0·05 level. Assuming at 27% incidence of bleeding complications in the group receiving heparin, a trial of this size would detect a 12% difference in bleeding complications with the same power. The design allowed for two interim analyses at 100 and 200 patients by an independent ethics monitoring group, with "stopping rules" set at patency rates of 80% and ≤50% for the heparin and placebo group respectively for the first analysis and 80% and ≤60% for the second analysis (p = 0·02). During the course of the trial it became apparent that the pooled patency rate at 48–120 hours for the first 200 patients was of the order of 78%—that is, either the patency rates for heparin and no heparin were very similar, or the initial patency rate estimate had been pessimistic. The steering committee, without itself having access to the unblinded data but having asked the chairman of the independent ethics monitoring group to review the safety data on approximately 300 patients and confirm that there were no *ethical* objections to continuing the study, then decided to extend the trial to include 650 patients. It is accepted that *any* alteration in trial size after the start of a trial might increase the risk of a type 1 error, but we though this was more than compensated by the increase in precision resulting from an increase in trial size.

Table 2 Perfusion and infarct related stenosis grades at 48–120 hour angiography

	Placebo	*Heparin*
No angiography performed	21	14
Infarct related vessel not identifiable	15	9
Angiography not between 48 and 120 hours	31	36
Perfusion grades (TIMI) (%):		
Non-perfusion (0)	58 (22·9)	32 (12·1)
Minimal perfusion (1)	6 (2·4)	12 (4·5)
Partial perfusion (2)	21 (8·3)	21 (7·9)
Complete perfusion (3)	168 (66·4)	200 (75·5)
Stenosis grades (%):		
Total occlusion	58 (22·9)	32 (12·1)
91–99% stenosis no complete filling	14 (5·5)	21 (7·9)
91–99% stenosis complete filling	47 (18·6)	41 (15·5)
50–90% stenosis	118 (46·6)	152 (57·4)
<50% stenosis	16 (6·3)	19 (7·2)

Risk ratio for non or minimal perfusion (TIMI 0 or 1) = 0·66 (95% confidence interval 0·47 to 0·93)

Risk ratio for functional occlusion (stenosis grade 5 or 6) 0·7 (95% confidence interval 0·52–0·96)

TIMI perfusion grades: 0 = no perfusion; 1 = penetration with minimal perfusion; 2 = Partial perfusion; 3 = Complete perfusion. ECSG stenosis grades: 0 = normal vessel; 1 = <50% diameter stenosis; 2 = diameter stenosis between 50 and 90% with complete filling of distal vessel within three cardiac cycles; 3 = diameter stenosis between 50 and 90% without complete filling of distal vessel within three cardiac cycles; 4 = diameter stenosis >90% with complete filling of distal vessel within three cardiac cycles; 5 = diameter stenosis >90% without complete filling of distal vessel within three cardiac cycles; 6 = total occlusion.

STATISTICAL EVALUATION

Relative risks and 95% confidence intervals were calculated according to Gardner and Altman.[17] The Mann–Whitney U test was used to compare HBDH activities.

TRIAL ORGANISATION

The organisation, coordination, and ethical superivision structure of the trial is described in the appendix.

Results

PATIENT NUMBERS AND BASELINE CHARACTERISTICS

Six hundred and fifty two patients were registered and allocated to receive either heparin (n = 328) or heparin placebo (n = 324). Eight patients were excluded from analysis—six because of errors in labelling the trial medication in one participating hospital and two because case record forms were not returned. Two patients aged over 70 were included inadvertently and have been retained in the analysis. Table 1 lists the baseline characteristics of all analysable patients (n = 644). These characteristics were evenly distributed between the groups. Electrocardiographic entry criteria were verified by the clinical events committee: 11 placebo and 13 heparin group patients were judged not to have fulfilled the stipulated entry criteria but they were retained in the analysis. Six hundred and two patients continued their trial medication up to the time of angiography (or to 120 hours). Twenty one patients in each group stopped trial medication before angiography: four in the heparin and three in the placebo group died and 14 in the heparin and 12 in the placebo group stopped because of bleeding, recurrent chest pain, or other complications.

ANGIOGRAPHY

Central angiographic evaluation was perfor-

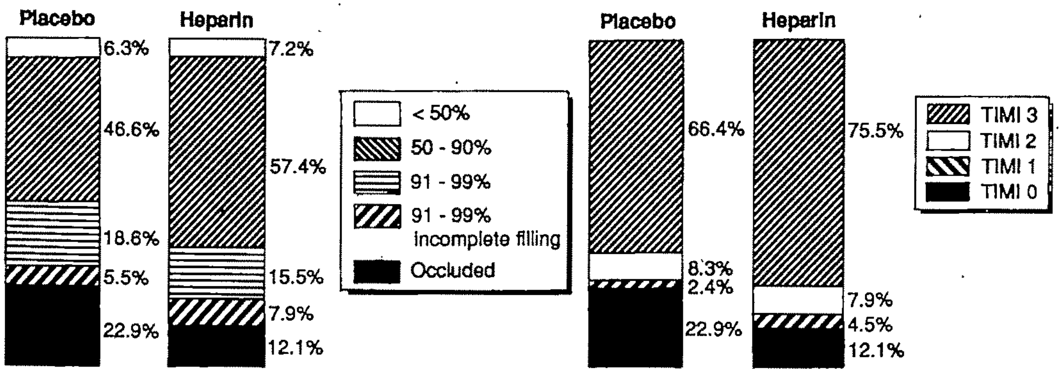

Figure 1 Histograms showing distribution of TIMI perfusion grades in infarct related vessels and ECSG stenosis grades in infarct related segments in patients who had angiography between 48 and 120 hours. (Grades are defined in the legend to table 2).

med on cine films from 609 patients (95%). No angiography was performed in 14 heparin group patients (death seven, complication two, refusal one, other reasons four) and 21 placebo group patients (death six, complication two, refusal six, other reasons seven).

The distribution of infarct related segments was evenly balanced between groups. Table 2 and figure 1 show the perfusion and stenosis grades of patients having angiography within the specified 48–120 hour interval. Figure 2 shows the relation between patency and the time that angiography was performed. There was no significant difference between the groups in the proportion of patients having angiography at different times. Patency, whether assessed by TIMI perfusion grades or by ECSG stenosis grades, was significantly better in patients allocated to heparin treatment. The relative risk of an occluded vessel (TIMI grade 0 or 1) at 48–120 hour angiography in the heparin group as compared with the placebo group was 0·66, with 95% confidence intervals of 0·47 to 0·93. The difference remains when *all* angiograms are considered (patency 83·7% for heparin group *v* 75·1% for placebo, relative risk of an occluded vessel 0·65, 95% C.I. 0·47 to 0·93). Imputing a closed vessel to all patients whose angiograms were not recorded does not alter the conclusion.

CLINICAL EVENTS AND REINFARCTION

Two hundred and sixty nine patients in the heparin group and 303 patients in the placebo group showed enzymatic evidence of myocardial infarction in the form of a rise in plasma creatine kinase to more than twice the normal activity. Two hundred and forty four patients in the heparin and 251 in the placebo groups developed new Q waves consistent with infarction. The trends towards reduced frequency of enzymatic evidence of infarction and of new Q waves in the heparin group were not statistically significant.

Table 3 shows the incidence of recurrent chest pain, clinical reinfarction, and mortality in the two treatment groups: events have been divided into those occurring between allocation and angiography and between angiography and discharge. There was no overall difference between heparin and placebo groups, but there was a non-significant trend towards fewer clinical ischaemic events in the period before angiography in the patients receiving heparin. A second dose of alteplase was given to 26 patients—11 allocated to heparin and 15 to placebo. Twenty one patients received 50 mg (eight heparin, 13 placebo) and five received 100 mg (three heparin and two placebo).

ENZYMATIC INFARCT SIZE

Enzymatic infarct size expressed as Q_{72} HBDH could be calculated from serial measurements in 258 placebo group and 246 heparin group patients. Mean Q_{72} HBDH was 672 units for the placebo group and 646 units for the heparin group ($p = NS$). We were able to use extrapolated values for missing measurements to calculate the infarct size for 309 placebo group and 304 heparin group patients: mean values for Q_{72} HBDH were 659 units and 646 units respectively ($p = NS$). Imputing "worst case" values to patients who had died gave estimates for 313 placebo group and 309 heparin group patients: 673 units *v* 646 units ($p = NS$). There was a trend towards reduced infarct size of about 4% in patients receiving heparin—this did not reach conventional significance levels. The Q_{24}/Q_{72} HBDH ratio (a measure of the rapidity of enzyme release) had mean values of 0·68 for 258 placebo group patients and 0·69 for 246 heparin group patients ($p = NS$).

BLEEDING COMPLICATIONS AND HAEMOSTATIC VALUES

Mean haemoglobin concentrations and haematocrit at admission and discharge did not

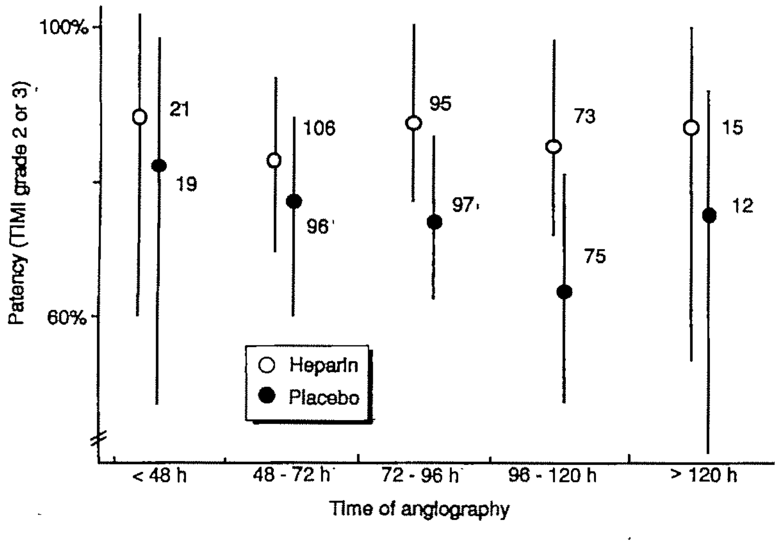

Figure 2 Means and 95% confidence intervals for TIMI grade 2 or 3 perfusion in angiograms performed at different times in heparin and placebo groups.

Table 3 Incidence of death, recurrent chest pain, and clinical reinfarction in heparin and placebo group patients between allocation and angiography and between angiography and hospital discharge

	Placebo (n=320) (%)	*Heparin (n=324) (%)*
Events between randomisation and angiography or 120 hours		
Death	2 (0·6)	4 (1·2)
Recurrent chest pain*	37 (11·6)	30 (9·3)
with ST elevation + enzyme rise	3 (0·9)	2 (0·6)
with ST elevation only	23 (7·2)	21 (6·5)
other	11 (3·4)	7 (2·2)
Intracranial bleeding	0	2 (0·6)
Other intracranial events	0	0
Other thromboembolic events	0	0
Events presenting after angiography or 120 hours		
Death	9 (2·9)	5 (1·6)
Recurrent chest pain*	30 (9·4)	31 (9·6)
with ST elevation + enzyme rise	7 (2·2)	8 (2·5)
with ST elevation only	20 (6·3)	22 (6·8)
other	3 (0·9)	2 (0·6)
Intracranial bleeding	0	0
Other intracranial events	1 (0·3)	2 (0·6)
Other thromboembolic events	1 (0·3)	3 (0·9)

*Recurrent chest pain occurring before angiography (<120 h) was assessed by the clinical events committee; after angiography (or >120 h) assessment is that of the investigator

differ significantly between groups. Mean haemoglobin at admission was 9·5 mmol/l in the heparin group (haematocrit 44·2%) and 9·6 mmol/l (haematocrit 44·1%) in the placebo group. The mean lowest haemoglobin concentration recorded during hospital admission was 8·3 mmol/l (haematocrit 37·9%) in the heparin group and 8·2 mmol/l (haematocrit 38·0%) in the placebo group.

Table 4 lists the incidence of bleeding complications occurring between allocation and angiography and between angiography and discharge. There was a non-significant trend towards more frequent bleeding complications in the heparin group. Both episodes of intracerebral bleeding were verified by computerised tomographic scanning and occurred in patients allocated to heparin. One patient developed a left hemiparesis nine hours after allocation and survived to leave hospital: the other developed symptoms 14 hours after randomisation and died after 19 days. One patient allocated to heparin developed neurological symptoms three hours before angiography and died five hours after angiography from cardiac rupture. He was found to have cerebral oedema and moderate subarachnoid bleeding at necropsy. Both the remaining events occurred after angiography and in patients allocated to placebo treatment. One had symptoms suggestive of a transient ischaemic attack five hours after angiography, was found to have a meningioma on computed tomography, and was discharged alive. The other had a transient ischaemic attack 60 hours after angiography and recovered completely.

Table 4 Incidence of bleeding complications between randomisation and angiography and between angiography and discharge

	Placebo (n=320) (%)	*Heparin (n=324) (%)*
Between randomisation and angiography:		
Total patients with bleeding complications (%):	48 (15·1)	57 (17·6)
Total number of bleeding complications	51	67
Haematoma at puncture site	25 (7·8)	32 (9·9)
Haematoma at other site	7 (2·2)	7 (2·2)
Prolonged bleeding after puncture	5 (1·6)	5 (1·6)
Prolonged bleeding at other site	1 (0·3)	1 (0·3)
Retroperitoneal bleed	1 (0·3)	0
Haemoptysis	0	2 (0·6)
Haematemesis	4 (1·3)	0
Haematuria	2 (0·6)	8 (2·5)
Gingival	5 (1·6)	5 (1 6)
Melena	0	0
Intracranial bleed	0	2 (0·6)
Other	1 (0·3)	5 (1·6)
Between angiography and discharge:		
Total patients with bleeding complications (%):	9 (2·8)	16 (4·9)
Total number of bleeding complications	14	16
Haematoma at puncture site	9 (2·8)	9 (2·8)
Haematoma at other site	1 (0·3)	1 (0·3)
Prolonged bleeding after puncture	0	2 (0·6)
Prolonged bleeding at other site	0	0
Retroperitoneal bleed	0	0
Haemoptysis	0	0
Haematemesis	2 (0·6)	0
Haematuria	0	2 (0·6)
Gingival	0	0
Melena	1 (0·3)	0
Intracranial bleed	0	0
Other	1 (0·3)	2 (0·6)

LEFT VENTRICULAR THROMBUS

Echocardiographic assessment of left ventricular thrombus was attempted in 613 patients. The central assessment committee decided that 532 echocardiograms were technically adequate for assessment. Left ventricular thrombus was present in 10 patients (3·7%) allocated to heparin and in 18 patients (6·8%) allocated to heparin placebo (relative risk 0·55, 95% CI 0·26 to 1·16).

Discussion

The present study shows that patients treated with intravenous alteplase, oral or intravenous aspirin, and concomitant intravenous heparin had a higher coronary patency rate at 48–120 hours than patients randomised to receive alteplase, aspirin, and heparin placebo. These results are consistent with two previous smaller studies that also reported enhanced patency in patients receiving heparin after alteplase thrombolysis,[12 13] although the absolute difference in patency was less pronounced in the present study. Coronary patency after thrombolysis depends on two competing time-dependent processes—one tending to increase perfusion as a consequence of ongoing thrombolytic activity and the other to reduce it as a result of continuing fibrin deposition. There is no single time point at which angiography will give a complete picture of the dynamic balance between patency and occlusion. Despite considerable differences in early patency it has previously been shown that late (10–22 day) angiography shows little difference in coronary patency between patients treated with a thrombolytic agent and patients receiving either a placebo or non-thrombolytic treatment such as heparin + aspirin or heparin + nitrates;[18] it is likely that angiography in the 48–120 hour time window will underestimate rather than overestimate real differences in perfusion over the first 24 hours after thrombolysis. Another difference between the present study and other trials is that we gave a relatively large initial dose of aspirin.

The difference in perfusion rates between heparin and placebo groups was similar in angiograms performed at different times within the 48–120 hour period. The number of angiograms performed before 48 hours was small, and in these patients early angiography was usually performed for clinical indications such as recurrent chest pain. The National Heart Institute of Australia study showed that patients randomised 24 hours after the start of thrombolytic therapy to continue receiving intravenous heparin or to receive aspirin plus dipyridamole had similar coronary patency rates at one week,[19] and it is possible that any beneficial effects of the additional anticoagulation provided by heparin are shown only within the first 24 hours.

There was a trend towards a smaller enzymatic infarct size in the heparin group but this did not reach conventional significance levels. The difference in enzymatic infarct size measured by similar techniques in a previous study comparing alteplase plus heparin and aspirin with placebo plus heparin and aspirin, in which the differences in early patency would be expected to be much greater, was 20%.[3] No mortality difference between the treatment groups was seen and overall mortality was low. It is possible that patients recruited to the present study might not be fully representative of the whole myocardial infarct population. This does not invalidate the conclusions about patency rates, but it might account for the low mortality and morbidity observed. A tendency to bias recruitment towards less seriously ill patients might also dilute any expected difference in infarct size. There was no overall difference in the incidence of reinfarction between the heparin and placebo groups, although there was a non-significant trend towards a more frequent recurrence of ischaemia in the placebo group between allocation and angiography. Similarly, there was no significant difference in the incidence of major haemorrhagic or thromboembolic events. However, the precision with which a trial of this size can predict the true incidence of rare events such as cerebral haemorrhage is limited. The prevalence of echocardiographically detected left ventricular thrombus was low in both groups, with more thrombi in the placebo group but with 95% confidence intervals for relative risk including zero.

Do the results of the present study affect the interpretation of the recently completed GISSI 2[15] and International Study Group[16] trials comparing streptokinase and alteplase? These protocols randomised patients receiving alteplase and aspirin either to no heparin or to subcutaneous heparin starting at 12 hours and showed no effect of heparin either on a "combined outcome" measure or on survival. We cannot say whether the GISSI 2 and International Study Group results would have been different had alteplase been combined with intravenous heparin, but in the light of this and other smaller trials it seems that the alteplase-alone regimen used was not optimal in terms of restoring coronary patency. The relation between coronary patency and outcome has been disputed, but not disproved, and it seems likely from our present data that the patency rates achieved with alteplase alone would be very similar to those expected, on the basis of previous trials,[5 6] with streptokinase.

No direct evidence has been presented that the delayed subcutaneous heparin regimens used in the GISSI 2 and International Study Group trials are comparable with the intravenous heparin regimen used in the present study and in several previous trials. High dose subcutaneous heparin is capable of inducing systemic anticoagulation, but there is a delay between its initiation and an optimal anticoagulant effect, and the lack of benefit from heparin in the GISSI 2 and International Study Group trials may have been a result of the specific regimen used.[20] Possible mechanisms for a beneficial effect of early intravenous heparin have been reviewed by White,[21] and it seems likely that aspirin even in relatively high dosage is not a complete substitute.

It is clear that we still have an incomplete understanding of the best way to control the thrombotic process after successful thrombolysis. The present study suggests that early treatment with intravenous heparin does indeed contribute to the efficacy of alteplase thrombolysis.

Appendix 1

PARTICIPATING CENTRES AND PHYSICIANS

Medisch Centrum Alkmaar, Netherlands, (C Burgersdijk, A E R Arnold); University Clinics, Basel, Switzerland, (M Pfisterer); Hospital Mutua de Terrassa, Barcelona, Spain, (L Saenz Cusi); Hospital de la Santa Creu, Barcelona, Spain, (J Garcia Picart, M Garcia Moll); Hospital Clinico y Provincial, Barcelona, Spain, (A Betriu); Thoraxcentrum, Academisch Ziekenhuis Dijkzigt, Rotterdam, Netherlands, (M L Simoons); Leyenburg Ziekenhuis, Den Haag, Netherlands, (G A van der Kley); Hôpital St Luc, Brussels, Belgium, (J Col); Royal Infirmary, Edinburgh, (D de Bono, P Bloomfield); Hospital de Santa Cruz, Lisbon, Portugal, (R Seabra Gomes); Hospital Gregorio Maranon, Madrid, Spain, (L Lopez Bescos); Imelda Ziekenhuis, Bonheiden, Belgium, (G Verstreken); Hart Ziekenhuis, Tienen, Belgium, (L de Wolf); Algemeen Ziekenhuis St Jozef, Mechelen, Belgium, (H van Brabandt); Spaarne Ziekenhuis, Heemstede, Netherlands, (H H Kruyswijk); Spaarne Ziekenhuis, Haarlem, Netherlands, (E Mueller); Hospital Universario, Alcala de Herares, Madrid, Spain, (M Sanchez Garcia); Hospital La Paz, Madrid, Spain, (L Lopez Sendon, L Martin Jadraque); Ziekenhuis "De Weezenlanden", Zwolle, Netherlands, (F Zijlstra).

Appendix 2

TRIAL ORGANISATION

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Ethical and Data Monitoring Committee

Chairman—D Wood (Southampton); *Members*—J Hampton (Nottingham), L Wilhelmsen (Goteborg), W Scharper (Bad Nauheim), D Julian (London).

Angiographic Assessment

D de Bono (Leicester), A Betriu (Barcelona), C Burgersdijk (Alkmaar), M J B van den Brand (Rotterdam), E Benit (Leuven).

Clinical Events and ECG Assessment Committee

J L Willems (Leuven), M L Simoons (Rotterdam), M Pfisterer (Basel).

Echo Assessment

G Sutherland (Rotterdam), B Denef (Leuven), J A Henneman (Alkmaar).

Core laboratory for enzyme analysis

G Willems, W T H Hermans, B Kop (Research Institute for Cardiovascular Diseases, Maastricht, Netherlands).

Core laboratory for haemostasis measurements

M Verstraete, J Arnout (Centrum voor Thrombose en Vasculair Onderzoek, Katholieke Universiteit Gasthuisberg, Leuven, Belgium).

Data centre

K M Hoolboom-Nijssen, I van Oosterom-de Waard, L Jamine, Y Koppelaars, J C Kelder, L Muller, J Tijssen, L Rodenburg (Westzeedijk 120, Rotterdam, Netherlands).

1 The TIMI study group. The thrombolysis in myocardial infarction (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985;312:932–6.

2 Verstraete M, Bleifeld W, Brower RW, *et al.* Double blind randomized trial of intravenous recombinant tissue type plasminogen activator versus placebo in acute myocardial infarction. *Lancet* 1985;ii:965–9.

3 Van de Werf F, Arnold AER. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. *BMJ* 1988;297:1374–8.

4 Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo Scandinavian Study of early thrombolysis (ASSET). *Lancet* 1988;ii:525–30.

5 Verstraete M, Bernard R, Bory M, *et al.* Randomized trial of intravenous recombinant tissue type plasminogen activator versus intravenous streprokinase in acute myocardial infarction. *Lancet* 1985;i:842–7.

6 Chesebro JH, Knatterud G, Roberts R, *et al.* Thrombolysis in myocardial infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987;76: 142–54.

7 Chesebro JH, Knatterud G, Braunwald E. Thrombolytic therapy [letter]. *N Engl J Med* 1988;319:1544–5.

8 The TIMI Research Group. Immediate versus delayed catheterisation and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI–IIA results. *JAMA* 1988;260:2849–58.

9 TIMI study group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1989;320:618–28.

10 Topol EJ, Morris DC, Smalling RW, *et al.* A multicentre, randomized, placebo controlled trial of a new form of intravenous recombinant tissue type plasminogen activator in acute myocardial infarction. *J Am Coll Cardiol* 1987;9:205–13.

11 Topol EJ, George BS, Kereakis DJ, *et al.* A randomised controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989;79:281–6.

12 Bleich SD, Nichols T, Schumacher R, *et al.* Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;66:1412–7.

13 Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1990;323:1433–7.

14 Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. GISSI 2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;336:65–71.

15 The International Study Group. In hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990;336:71–5.

16 van der Laarse A, Hermans WT, Hollaar L, *et al.* Assessment of myocardial damage in patients with acute myocardial infarction by serial measurement of serum alpha hydroxybutyrate dehydrogenase. *Am Heart J* 1984;107:248–60.

17 Gardner MJ, Altman DG. *Statistics with confidence.* London: British Medical Journal, 1989.

18 Rentrop KP, Feit F, Sherman W, Thornton JC. Serial angiographic assessment of coronary obstruction and collateral flow in acute myocardial infarction. Report from the second Mount Sinai/New York University Reperfusion Trial. *Circulation* 1989;80:1166–75.

19 National Heart Foundation of Australia Coronary Thrombolysis Group. A randomised comparison of oral aspirin/dipyridamole versus intravenous heparin after rt-PA for acute myocardial infarction [abstract]. *Circulation* 1989;80:II–114.

20 Collins R, Flather M, Peto R. GISSI 2: 10% reduction in mortality with heparin in myocardial infarction? *Lancet* 1990;336:439–50.

21 White HD. GISSI 2 and the heparin controversy. *Lancet* 1990;336:297–8.

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PRECAUTIONS: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia; possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with anti-hypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response in Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.

SIDE EFFECTS: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.

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Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

REFERENCES: 1. White WB, Dey HM and Schulman P. Am Heart J 1989; **118:** 782-795. **2.** Kannel WB. Am J Med 1983; **75:** 4-11.

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FUNCTION: Liver function tests should be performed periodically, discontinue if elevated liver enzymes greater than 3 ti
the upper limit of normal persist. Caution should be exercised in patients with a history of liver disease or alcoholism. Incre
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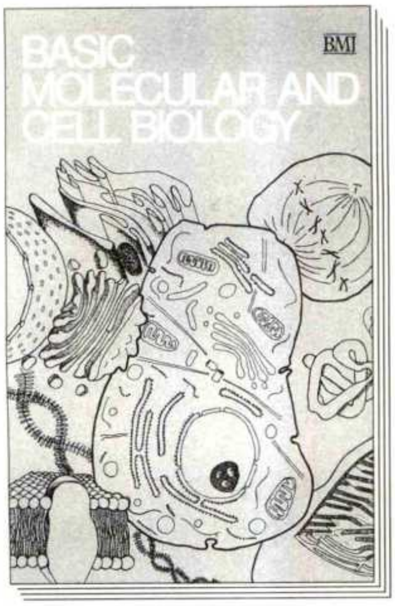

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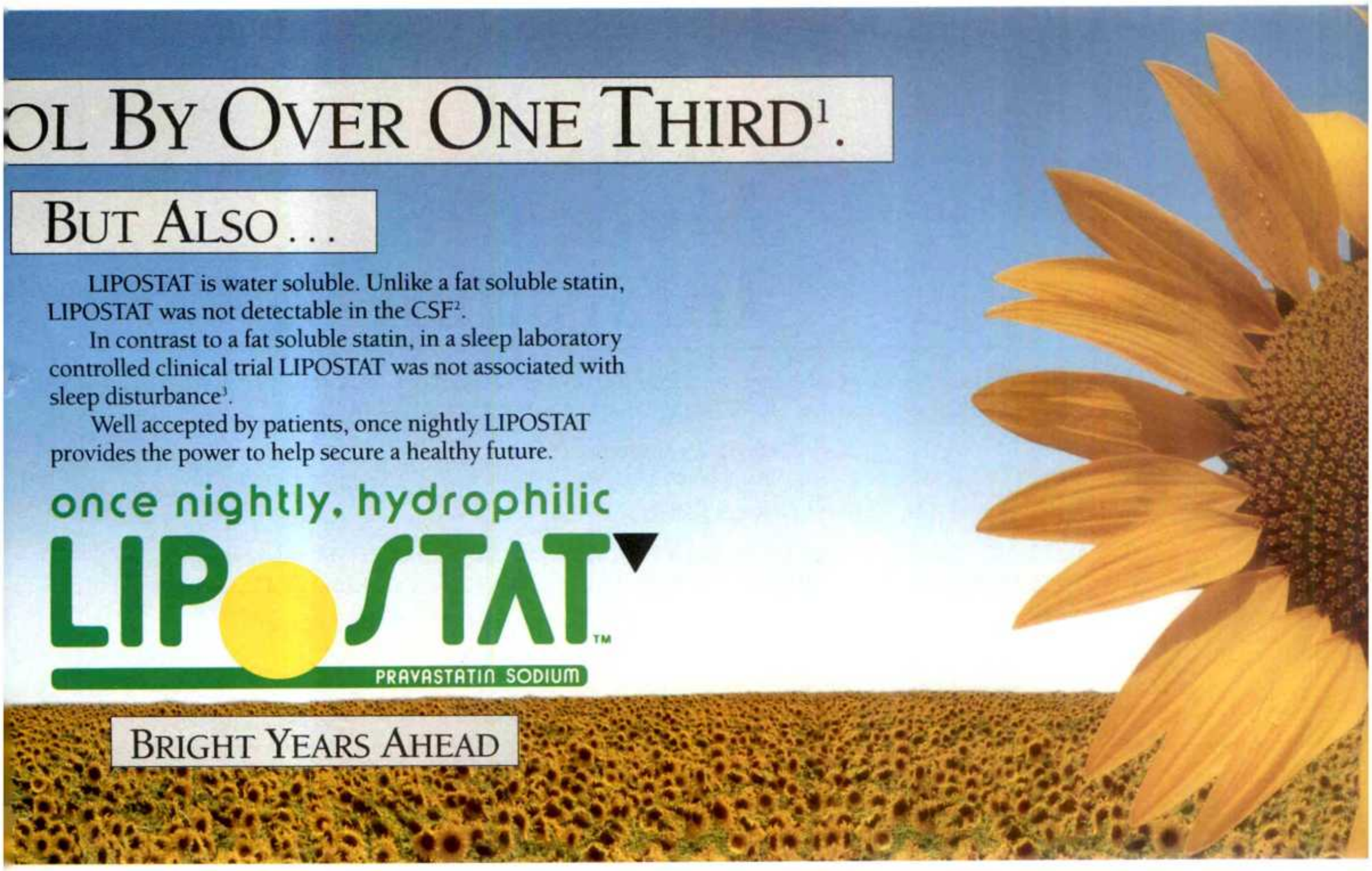

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References
1. Data on file. In trials LIPOSTAT demonstrates an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).
2. Botti RE et al. Clin Neuropharm 1991; 14 (3): 256-261.
3. Bixler EO. Round Table Discussion, Lipid Management, Pravastatin and the Differential Pharmacology of HMG-CoA Reductase Inhibitors. Proceedings of a panel discussion held in London on 5th July 1989. Royal Society of Medicine Services Round Table Series 1990; 16: 32-40.

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ASSESSMENT OF SIGNAL AVERAGED ELECTROCARDIOGRAM

This was recorded by a commercially available system (Arrhythmia Research Technology, model 1200EPX) as described elsewhere.[22] The high pass filter was set at 25 Hz and 100–200 beats were averaged to achieve a noise level of less than 0·4 μV. Recordings were made at day six or seven in all patients in sinus rhythm. Late potentials were considered to be present if any two of the following criteria were present: filtered QRS complex $>$ 120 ms, root mean square voltage during the last 40 ms of the filtered QRS complex $<$ 25 μV, and duration of the filtered QRS complex of $>$ 40 ms after voltage fell below 40 μV.

CORONARY ANGIOGRAPHY

Coronary angiography was performed in all patients with a positive exercise test before discharge. The number of coronary arteries with significant stenoses of the luminal diameter ($>$50%) was noted and patency of the infarct artery according to the Thrombolysis in Myocardial Infarction Trial (TIMI) scale was recorded. Left ventricular ejection fraction was calculated with the *Mac angio package* (Dodge formula) using the right anterior oblique view. In those patients who did not undergo angiography the ejection fraction was calculated using radionuclide scanning. A left ventricular ejection fraction $<$ 40% was considered abnormal.[4]

STATISTICAL ANALYSIS

Results were compared using the two tailed Student's t test and the χ^2 test with Yates' correction where appropriate. A multiple ANOVA procedure was used to assess the influence of age and left ventricular function on the relation between baroreflex sensitivity and clinical events. Homogenicity of variance was assessed by Cochran's C test. To assess the relation between baroreflex sensitivity and continuous variables simple linear regression was fitted. All results are expressed as mean (SD) with 95% confidence intervals (95% CIs) where appropriate. Statistical significance was assumed for $p < 0·05$. The standard definitions for sensitivity, specificity, and positive and negative predictive accuracy were used. Relative risk was defined as the ratio event rate in patients with a positive test:event rate in patients with a negative test.

Results

The test group consisted of predominantly men; only five women were included and the mean age of the population was 56 (9·3) years. There was a roughly equal distribution of anterior and inferior infarcts (64 *v* 58) but a preponderance of Q wave infarcts (82 *v* 40). Each patient has been followed up for a minimum of one year after infarction and the results presented apply to events occurring in this year. During this time there were 13 deaths and 10 documented life threatening arrhythmic events (five patients died suddenly and five others were readmitted with sustained ventricular arrhythmias).

Twenty four per cent of patients were discharged on oral β blockade. Coronary revascularisation was performed in 22% of patients (angioplasty or coronary vein grafting) and five patients received antiarrhythmic drugs after clinical arrhythmic events.

There were no major complications after baroreflex sensitivity testing. In particular, no patient developed signs or symptoms of myocardial ischaemia or serious ventricular arrhythmias and arterial cannulation of the femoral and radial arteries was not associated with any complications. Minor symptoms were common, however, after administration of phenylephrine, with over 95% of the patients experiencing either transient headaches and circumoral or facial paraesthesia. In five patients, not reported here, we were unable to obtain satisfactory baroreflex sensitivity recordings. This was due to frequent ventricular extrasystoles during the test (three cases), the development of pulsus alternans (one case), and paroxysmal episodes of atrial flutter (one case).

Baroreflex sensitivity for the whole population was 7·39 (4·68) ms/mm Hg and there was a significantly inverse correlation with age ($r = -0·68$, $p < 0·001$) (fig 2). No difference was noted in baroreflex sensitivity according to anterior infarction (7·36 (5·05) *v* 6·78 (5·12) ms/mm Hg, 95% CI $-$ 0·23 to 0·36 NS) or the use of thrombolytic agents (7·98 (5·3) *v* 6·78 (3·9) ms/mm Hg, 95% CI $-$ 0·9 to 1·5 NS).

BAROREFLEX SENSITIVITY, EJECTION FRACTION, AND CORONARY ARTERY DISEASE

The mean left ventricular ejection fraction in the study group was 51% (14·4%). Baroreflex

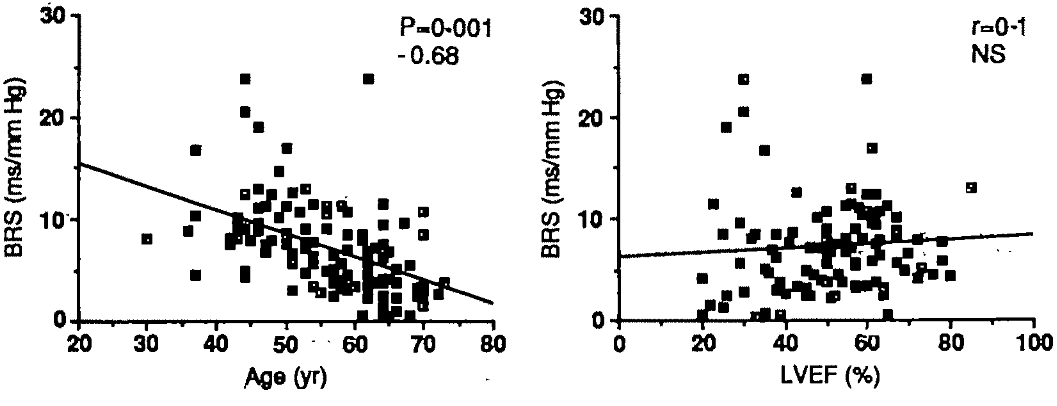

Figure 2 Plot of relation between baroreflex sensitivity (BRS) and left ventricular ejection fraction (LVEF), and age.

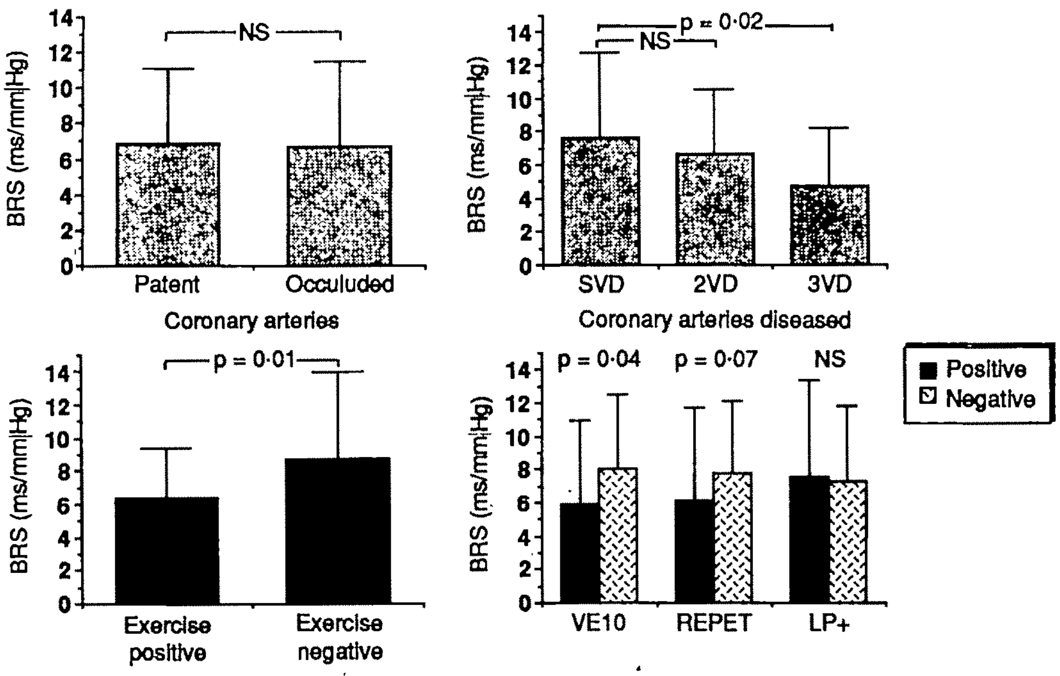

Figure 3 Column graphs (mean (SD)) of relation between baroreflex sensitivity (BRS), coronary artery patency, number of coronary arteries diseased (SVD = single vessel disease etc), results of exercise test, more than 10 ventricular extrasystoles per hour (VE 10), ventricular repetitive forms (REPET), and late potentials (LP+).

sensitivity was not correlated with left ventricular ejection fraction (r = 0·1, NS) (fig 2). Of the 83 patients catheterised 38 had single vessel disease, 26 had two vessel disease, and 19 three vessel disease. Baroreflex sensitivity was lowest in patients with three vessel disease (4·76 (3·5) ms/mm Hg) and this was significantly lower than in patients with single vessel disease (7·66 (5·1) ms/mm Hg *v* 4·76 (3·5) ms/mm Hg, 95% CI 0·34 to 5·5, p = 0·02) but not two vessel disease (6·7 (3·86) *v* 4·76 (3·5) ms/mm Hg, 95% CI – 0·3 to 4·1, p = 0·08). Infarct artery patency (TIMI grade 2 or greater) did not appear to affect baroreflex sensitivity (6·87 (4·23) *v* 6·72 (4·71) ms/mm Hg, 95% CI – 1·9 to 2·2) (fig 3).

BAROREFLEX SENSITIVITY AND EXERCISE TESTING

In 71 patients the exercise test was considered positive. The mean peak heart rate at exercise for the whole group was 136 (18·2) beats/min, mean exercise duration was 6·26 (2·12) min, and the mean workload achieved was 7·18 (2·51) MET. Baroreflex sensitivity appeared to be significantly lower in those patients with a positive exercise test (6·39 (4·0) *v* 8·74 (5·2) ms/mm Hg, 95% CI 0·7 to 4·0, p = 0·01) and weak but significant correlations were noted between baroreflex sensitivity and workload expressed in METs (r = 0·34, p < 0·0002), exercise duration (r = 0·33, p < 0·0003), and the peak heart rate achieved at exercise (r = 0·23, p = 0·02).

BAROREFLEX SENSITIVITY, 24 HOUR ELECTROCARDIOGRAPHIC RECORDINGS AND THE SIGNAL AVERAGED ELECTROCARDIOGRAM

Frequent ventricular extrasystoles (> 10/h) were noted on long term electrocardiographic recordings in 37 patients and in these patients baroreflex sensitivity was significantly lower (5·9 (5·01) *v* 7·99 (4·5) ms/mm Hg, 95% CI 0·3 to 3·9, p = 0·04). In 28 patients repetitive ventricular forms were noted but baroreflex sensitivity though lower was not significantly so (6·07 (5·57) *v* 7·74 (4·4) ms/mm Hg, 95% CI – 0·4 to 3·7, p = 0·07). The signal averaged electrocardiogram was considered positive in 22 patients but again no difference was noted in baroreflex sensitivity (7·5 (5·9) *v* 7·3 (4·5) ms/mm Hg, 95% CI – 2·2 to 2·4, NS).

RELATION OF BAROREFLEX SENSITIVITY TO TEST VARIABLES

In the study population the mean change in systolic blood pressure was 28·5 (range 15 to 36) mm Hg, and the mean dose of phenylephrine used was 0·32 mg. No correlation was noted between baroreflex sensitivity and test variables such as the dose of phenylephrine used (r = 0·04) or the subsequent rise in systolic blood pressure (r = – 0·014) but there was a weak correlation between baroreflex sensitivity and the resting heart rate or RR interval (r = 0·282, p = 0·001). We found a significant correlation between baroreflex sensitivity and the maximum change in RR interval (r = 0·513, p = 0·001), but this was not as strong as might have been expected. In several patients, abrupt rather than gradual changes in heart rate occurred during the phenylephrine test (fig 4).

HEART RATE VARIABILITY AND BAROREFLEX SENSITIVITY

For the whole study group the mean value of the SDRR was 100 (40) ms, heart rate variability index was 26·76 (10·33) ms, rMSSD was 29·41 (14·66) ms, pNN50 was 6·76 (8·7), and the mean RR interval was 845 (144) ms. As heart rate variability and baroreflex sensitivity are reputed measures of vagal tone, it might be expected that strong correlations would exist between these measures. In fact no correlation was noted between any temporal measure of heart rate variability (SDRR, rMSSD, pNN50, or the heart rate variability index) and

Prognostic value of baroreflex sensitivity testing after acute myocardial infarction

T G Farrell, O Odemuyiwa, Y Bashir, T R Cripps, M Malik, D E Ward, A J Camm

Abstract

***Background*—Disturbances of autonomic function are recognised in both the acute and convalescent phases of myocardial infarction. Recent studies have suggested that disordered autonomic function, particularly the loss of protective vagal reflexes, is associated with an increased incidence of arrhythmic deaths. The purpose of this study was to compare the value of differing prognostic indicators with measures of autonomic function and to assess the safety of arterial baroreflex testing early after infarction.**

***Methods*—As part of a prospective trial of risk stratification in post-infarction patients arterial baroreflex sensitivity, heart rate variability, long term electrocardiographic recordings, exercise stress testing, and ejection fraction were recorded between days 7 and 10 in 122 patients with acute myocardial infarction.**

***Results*—During a one year follow up period there were 10 arrhythmic events. Baroreflex sensitivity was appreciably reduced in these patients suffering arrhythmic events (1·73 SD (1·49) *v* 7·83 (4·5) ms/mm hg, 95% confidence interval (CI) 4·8 to 7·3, $p = 0{\cdot}0001$). Significant correlations were noted with age ($r = -0{\cdot}68$, $p < 0{\cdot}001$) but not left ventricular function. When baroreflex sensitivity was adjusted for the effects of age and ventricular function baroreflex sensitivity was still considerably reduced in the arrhythmic group (2·1 *v* 7·57 ms/mm Hg, $p < 0{\cdot}0001$). Depressed baroreflex sensitivity carried the highest relative risk for arrhythmic events (23·1, 95% CI 7·7 to 69·2) and was superior to other prognostic variables including left ventricular function (10·4, 95% CI 3·3 to 32·6) and heart rate variability (10·1, 95% CI 5·6 to 18·1). No major complications were noted with baroreflex testing and in particular no patients developed ischaemic or arrhythmic symptoms during the procedure.**

***Conclusions*—Disordered autonomic function as measured by depressed baroreflex sensitivity or reduced heart rate variability was associated with an increase incidence of arrhythmic events in post-infarction patients. Baroreflex testing can be safely performed in the immediate post-infarction period.**

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Established methods of risk stratification in post-infarction patients are based on clinical features; exercise stress testing; and the identification of complex ventricular arrhythmias, impaired left ventricular function, and multivessel coronary artery disease.[1-4] Despite such diverse approaches many problems associated with the identification and treatment of patients at high risk of malignant arrhythmias and sudden death remain unsolved. In an attempt to improve the prediction of arrhythmic events, novel methods of risk stratification including the signal averaged electrocardiogram[5] and programmed ventricular stimulation[6] have been evaluated. More recently, with growing awareness of the key role of neural mechanisms in arrhythmogenesis, attention has been focussed on the prognostic value of autonomic function tests such as heart rate variability analysis and baroreflex sensitivity.[7-10]

It has long been recognised that pronounced disturbances of autonomic function are seen in the acute phase of myocardial infarction and during the subsequent convalescent period.[11 12] Evidence from human and animal studies suggests that the preservation of vagal reflexes post-infarction protects against the induction of life threatening ventricular arrhythmias[13-15] and two groups have now reported on the value of heart rate variability in risk stratification.[16 17] To date, there has only been one report on the value of arterial baroreflex testing[18] performed one month after myocardial infarction. The purpose of this study was to test the feasibility, safety, and prognostic significance of baroreflex sensitivity testing early after infarction and to compare its value with other novel and established prognostic variables.

Patients and methods

STUDY POPULATION

We studied 122 patients admitted to St George's Hospital with an acute myocardial infarction. Patients over the age of 70 years or those with coexisting valvar heart disease, insulin dependent diabetes, arterial hypertension (> 160/90 mm Hg), atrial fibrillation, or evidence of sinoatrial disease were excluded. No digitalis or angiotensin converting enzyme inhibitors were used in the study group and β blockade was stopped at least 48 hours before study. Informed consent was obtained from all patients. The end points in the study were cardiac death and life threatening arrhythmic events including sudden death (Cardiac Arrhythmia Pilot Study definition[19]). Sixty eight of the patients were also included in another study on autonomic function and the inducibility of arrhythmias at programmed stimulation.[13]

BAROREFLEX SENSITIVITY TESTING

Baroreflex sensitivity was assessed by a previously described method.[20] All patients were studied in a fasting and supine state between days 7 and 10 (mean 8·2 days). A right femoral line (French gauge 8) was used to record continuous arterial pressure with simultaneous recording of a single elctrocardiogram lead at 25 mm/s. In 11 cases a radial line (French gauge 14) was used. After a period of rest when both blood pressure and heart rate values were stable a bolus of phenylephrine was injected intravenously over 15 seconds via a peripheral vein. An initial test dose of 0·2 mg was given, followed by progressively larger doses until a rise in systolic blood pressure of between 15 and 40 mm Hg was obtained. The test was repeated until at least three recordings were made using the optimum bolus dose. Baroreflex sensitivity was calculated by plotting the beat to beat change in RR interval against the beat to beat change in systolic blood pressure (baseline systolic – preceding systolic blood pressure). A linear regression analysis of these points was performed for the first sustained rise in blood pressure and baroreflex sensitivity was then estimated as the value of the slope from the regression analysis.

Only regression lines with a correlation coefficient greater than 0·8 were accepted for analysis. At least three such slopes were calculated for each patient and the mean of these was taken as the baroreflex sensitivity and expressed in ms/mm Hg. During the procedure patients were asked to breathe at a normal rate and to avoid slow or forced respiration. According to the work of La Rovere *et al* a baroreflex sensitivity of less than 3·0 ms/mm Hg was considered depressed.[18] Figure 1 shows examples of normal and depressed baroreflex sensitivity in post-infarction patients.

ANALYSIS OF 24 HOUR ELECTROCARDIOGRAPHIC RECORDINGS

All of the Holter tapes in the sample population were analysed using the Marquette 8500 scanner running version 5·7 of the Marquette arrhythmia analysis program allowing detection of normal sinus beats and supraventricular and ventricular extrasystoles. After automatic analysis of the tape, the data file was visually reviewed and edited by three of us (TF, YB, OO). In particular the histogram of normal to normal RR intervals was reviewed and the 20 longest and 20 shortest RR intervals were examined to ensure correct recognition. More than 10 extrasystoles in any one hour was regarded as abnormal on the basis of the MPIS study.[4]

HEART RATE VARIABILITY ANALYSIS

Heart rate variability analysis was performed by running the Marquette heart rate variability analysis program. Four methods of temporal domain analysis were used: the standard deviation (SD RR) and root mean square successive difference (rMSSD) of all normal RR intervals, the percentage of all normal RR intervals exceeding the adjacent RR intervals by greater than 50% (pNN50), and the heart rate variability index were calculated. The method used to derive the heart rate variability index has been previously described[21] and involves the digitising of the whole 24 hour electrocardiographic recording at an analogue to digital (A:D) sampling rate of 128 Hz and transfer to a personal computer (IBM PC-AT). The frequency distribution of durations of normal to normal RR intervals is constructed and heart rate variability index is expressed in milliseconds as the baseline width of the distribution curve measured by the method of minimum square difference interpolation. This method is less liable to recording noise and misrecognition artefact.[21] On the basis of previous research, SDRR of less than 50 ms was considered depressed[16] and the heart rate variability index was dichotomised at 16 ms (mean minus 1 SD).

EXERCISE PROTOCOL

Each patient underwent a symptom limited exercise test before discharge. In most cases this was according to the Bruce protocol although in eight patients a modified Bruce protocol was used. Those patients unable to exercise for reasons such as early post-infarction angina or impaired ventricular function were considered to have a positive test. Exercise testing was considered positive if a patient developed anginal chest pain, ST segment depression of greater than 1·5 mm, a failure of systolic blood pressure to rise by greater than 10%, or inability to complete stage one of the exercise protocol.

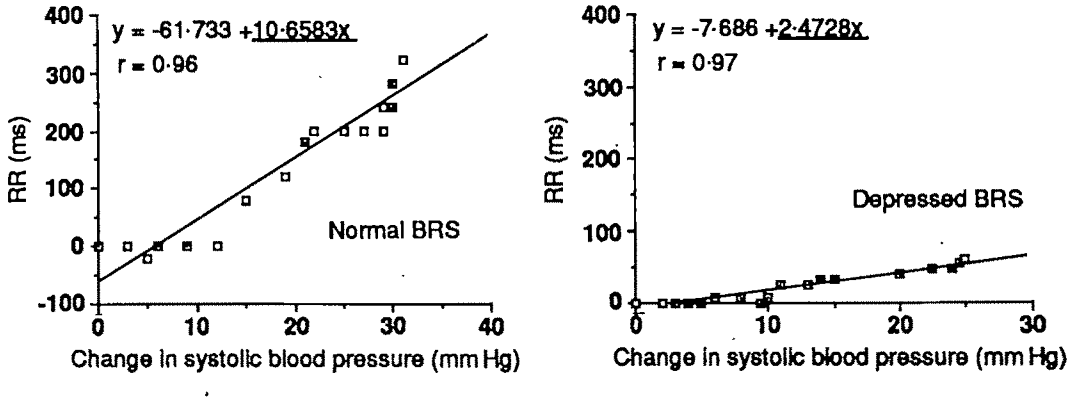


Figure 1 Examples of well preserved baroreflex sensitivity (10·65 ms/mm hg) and depressed (2·47 ms/mm Hg) in two patients after infarction. Baroreflex sensitivity (BRS) is expressed as gradient of regression line.

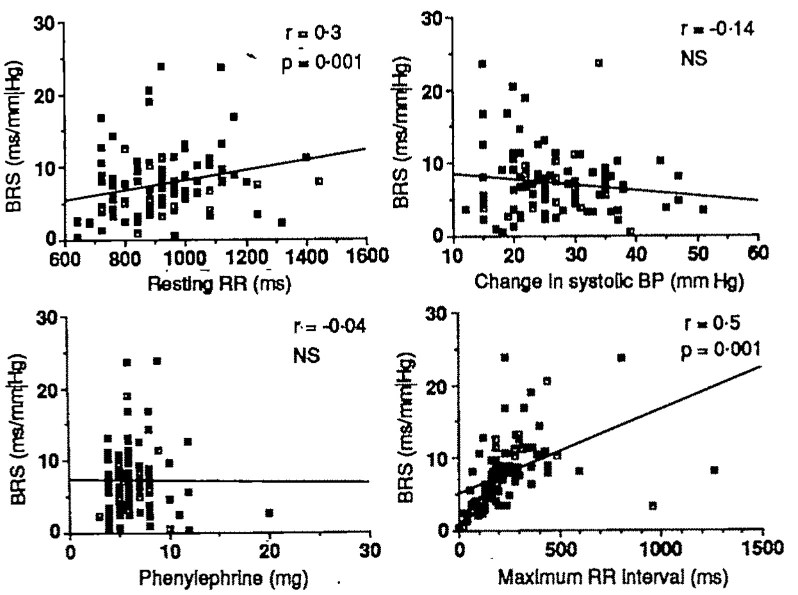
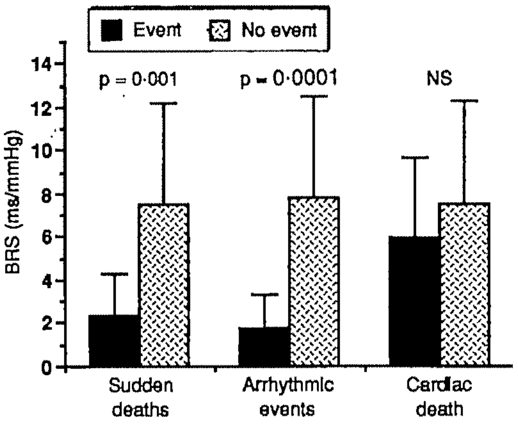


Figure 4 Plot of relation between baroreflex sensitivity (BRS) and variables associated with phenylephrine test including resting RR interval, change in systolic blood pressure, dose of phenylephrine used, and change in maximum RR interval.

Figure 5 Column graph (mean (SD)) of BRS according to clinical events. Arrhythmic events include sudden deaths and ventricular fibrillation.



baroreflex sensitivity. A weak correlation was noted, however, between the maximum RR interval change during baroreflex testing and the pNN50 index (r = 0·35, p = 0·04).

BAROREFLEX TESTING AND EVENTS

Baroreflex sensitivity was appreciably depressed in those patients (n = 10) suffering arrhythmic events including sudden death (1·75 (1·49) *v* 7·89 (4·53) ms/mm Hg, 95% CI 4·8 to 7·3, p = 0·0001) (fig 5). A MANOVA procedure was performed to assess the effects of age and left ventricular function on the relation between baroreflex sensitivity and arrhythmic events. After allowing for these possible influences, baroreflex sensitivity was still significantly reduced in patients suffering arrhythmic events (2·1 *v* 7·57 ms/mm Hg, p < 0·0001). Although age had a significant influence on the relation between baroreflex sensitivity and arrhythmic events (*t* value – 6·07, p < 0·0001), no such relation was noted for left ventricular function (*t* value – 1·650, NS) (table 1).

When we confined the analysis to patients suffering sudden death (n = 5), baroreflex sensitivity was still significantly lower (2·34 (1·9) *v* 7·54 (4·67), 95% CI 1·1 to 9·3, p = 0·001). When all cause cardiac mortality (n = 13) was considered, baroreflex sensitivity was lower but not significantly so (5·9 (3·78) *v* 7·49 (4·79), 95% CI – 1·14 to 4·3, NS).

COMPARISON OF BAROREFLEX SENSITIVITY, HEART RATE VARIABILITY, AND OTHER PROGNOSTIC VARIABLES IN THE PREDICTION OF ARRHYTHMIC EVENTS

The heart rate variability index (15·6 (6·5) *v* 27·8 (10·1) ms, 95% CI 9·8 to 15·4, p = 0·001), pNN50 (2·7 (2·94) *v* 7·2 (9·0)%, 95% CI 2·0 to 6·7, p = 0·005), and SDRR (60 (24) *v* 101 (37) ms, 95% CI 15 to 67, p = 0·001) were all significantly lower in patients suffering arrhythmic events. For all cause mortality only the heart rate variability index was significantly reduced (20·1 (7·6) *v* 27·6 (10·4) ms, 95% CI 1·6 to 14·3, p = 0·007). Table 2 summarises the results of investigations in patients suffering differing clinical events and table 3 gives the prognostic value of baroreflex sensitivity compared with differing measures of heart rate variability and other established prognostic variables. It can be seen that depressed baroreflex sensitivity is a superior predictor of arrhythmic risk compared with any other variable.

Discussion

Several studies have now drawn attention to the disturbances of autonomic tone that occur in both the acute and recovery phases of myocardial infarction.[10 11] More recently the role of heart rate variability, a non-invasive index of parasympathetic activity, in risk stratification has been examined in two large studies. These have led to the hypothesis that the impairment or loss of vagal reflexes may predispose to arrhythmic events or sudden deaths.[16 17] As the arterial baroreceptors are predominantly responsible for changes in heart rate it has been suggested that baroreflex sen-

Table 1 Results of MANOVA analysis

	DF	F Value	p Value	*Adjusted BRS means for the effects of age and LVEF* Observed mean (ms/mm Hg)	Adjusted mean (ms/mm Hg)
Arrhythmic event	1	15·7	< 0·0001	1·75	2·1
Covariates	2	18·79	< 0·0001		
Constant	1	54·69	< 0·0001		
No arrhythmic event				7·93	7·56

Regression for covariants: LVEF *t* = – 1·650; age *t* = – 6·097, p = 0·0001.
DF, degrees of freedom; LVEF, left ventricular ejection fraction; BRS, baroreflex sensitity.

Table 2 Summary of investigations according to clinical events

Event	*BRS (ms/mm Hg; mean (SD))*	*HRV SDRR (ms; mean (SD))*	*HRV index (ms; mean (SD))*	*LVEF% (mean (SD))*	*ETT (% positive)*	*SAECG (% positive)*	*VE10 (% positive)*
Sudden death (n = 5)	2·3 (1·9) *v* 7·5 (4·7)**	65 (26) *v* 99 (38)‡	17·9 (7·5) *v* 27·2 (10·3)†	33 (10 6) *v* 51·5 (14·1)§	80 *v* 58	60 *v* 16	80 *v* 28
Arrhythmic events (n = 10)	1·8 (1·5) *v* 7·9 (4·5)††	60 (24) *v* 101 (37)**	15·6 (6·5) *v* 27·8 (10·1)**	33 (9·4) *v* 52 (14)††	80 *v* 57	70 *v* 13	80 *v* 25
Cardiac death (n = 13)	5·9 (3·8) *v* 7·5 (4·8)	75 (39) *v* 100 (37)	20·1 (7·6) *v* 27·6 (10·4)¶	41 (18) *v* 52 (13·7)*	69 *v* 58	31 *v* 17	54 *v* 28

BRS, baroreflex sensitivity; HRV, heart rate variability; LVEF, left ventricular ejection fraction; ETT, exercise tolerance test; SAECG, signal averaged electrocardiogram; VE10, greater than 10 extrasystoles in any hour on long term electrocardiographic recording.
*p = 0·05; † p = 0·046; ‡ p = 0·04; § p = 0·02; ¶ p = 0·007; ** p = 0·001; †† p = 0·0001.

Table 3 Comparison of different prognostic variables in the prediction of arrhythmic events

Variable	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive accuracy (%)*	*Relative risk (95% CI)*
Exercise test positive	80	42·9	11	2·8 (1–8·9)
Late potentials	70	84·7	28	9·1 (3·9–20·9)
Ventricular ectopics > 10/h	80	75	22	20·6 (11–37·1)
Repetitive forms	80	82·1	28·6	13·4 (4·3–41·7)
HRV SD RR < 50 ms	60	94	55	10·4 (5·6–18·1)
HRV index < 16 ms	50	88·4	27·7	5·77 (3·0–11·1)
BRS < 3·0 ms/mm Hg	80	91	44	23·1 (7·7–69·2)
LVEF < 40%	80	76·8	23·5	10·4 (3·3–32·6)

BRS, baroreflex sensitivity; LVEF, left ventricular ejection fraction; HRV, heart rate variability; SD RR, standard deviation of normal RR intervals.

sitivity testing may provide a more sensitive and accurate assessment of autonomic function in patients after infarction. An earlier study from this department showed that depressed baroreflex sensitivity is associated with an increased induction of ventricular arrhythmias at programmed ventricular stimulation.[13] This finding is supported by the work of Schwartz and colleagues with a canine post-infarction model.[14,15]

The present study adds to an increasing body of evidence supporting a link between disordered autonomic function and sudden death. La Rovere *et al* have previously reported on the prognostic significance of baroreflex sensitivity testing in a smaller group of patients tested one month after myocardial infarction[18] and a strong correlation was noted between depressed baroreflex sensitivity and cardiovascular mortality but our present study is the first to have compared the value of baroreflex sensitivity and heart rate variability testing soon after infarction. This is particularly important as many arrhythmic events and sudden deaths occur in the immediate weeks after discharge.[19] By delaying the investigation, many events will be missed, consequently biasing the value of the test.

BAROREFLEX SENSITIVITY TESTING: TECHNICAL CONSIDERATIONS

Of particular importance is the finding that the phenylephrine method of baroreflex sensitivity assessment is safe and well tolerated in the immediate post-infarction period, although many patients did suffer transient minor side effects. Until recently the method was labour intensive and involved intra-arterial cannulation, consequently restricting its use in clinical practice. The development of reliable, non-invasive blood pressure monitoring by infrared photoplethysmography coupled with on line methods of analysis has largely solved these problems.

Baroreflex sensitivity seems to be independent of test related variables in the post-infarction population apart from a weak correlation with the resting RR interval.[18,20] Whereas these findings are similar to those of La Rovere *et al* they are at variance with previous studies in non-infarct patients.[23] Also, several patients in the present study had abrupt rather than the gradual changes in heart rate normally seen after the phenylephrine baroreflex test. These findings may represent further indirect evidence that the autonomic control of heart rate is disturbed after infarction. Care must be taken in extrapolating the results of baroreflex sensitivity testing in a controlled laboratory setting to a physiological state involving physical activity and ischaemic challenges. The baroreflex is not static, but instead exhibits dynamic resetting of its threshold, set point, and gain.[24] Other autonomic reflex arcs may also be important. For example, in the canine experiments performed by Schwartz and colleagues, those animals not liable to arrhythmias during ischaemic challenges not only exhibited well preserved baroreflex sensitivity but also pronounced heart rate changes during the ischaemic challenge, thought to be mediated by the Von Bezold-Jarisch reflex.[14]

BAROREFLEX SENSITIVITY AND CLINICAL CORRELATES

An important observation was the lack of correlation between baroreflex sensitivity and left ventricular ejection fraction, which has been noted previously.[18] This may at first seem surprising but reports of a relation between baroreflex sensitivity and ventricular function are confined to studies of congestive heart failure,[25] a condition that was absent in our patients at the time of testing. Left ventricular dysfunction may also manifest itself as abnormalities in wall motion and the resulting difference in wall stress might result in increased afferent sympathetic activity (particularly in anterior infarction where sympathetic fibres predominate). Although it has been suggested that baroreflex sensitivity may correlate better with regional wall motion abnormalities rather than a global index of ventricular function, a small pilot study has failed to support this hypothesis.[26]

Our finding that baroreflex sensitivity was lower in patients with a positive exercise test may be related to the classification of some tests as positive on the basis of poor exercise tolerance or haemodynamic response, particularly as there was a weak but significant correlation between baroreflex sensitivity and exercise duration/workload. Unlike La Rovere *et al* we did not find significant differences in baroreflex sensitivity according to infarct site or the presence of Q waves, although there are theoretical reasons why such differences may exist. The distribution of chemoreceptors and pressure receptors favours the inferoposterior region whereas parasympathetic fibres predominate in the subendocardial layer.[27 28] The precise anatomical location of infarcts and quantification into transmural and subendocardial infarcts on electrocardiographic criteria is known to be inaccurate, however, and previous studies have produced conflicting results. Webb *et al* found autonomic function to be significantly more depressed in anterior infarcts whereas La Rovere *et al* noted the reverse.[10 18]

The finding of a more pronounced depression of baroreflex sensitivity in patients with multivessel disease is also in agreement with previous studies of both baroreflex sensitivity[18] and heart rate variability[29] after infarction. No clear explanation for this finding is available, but multivessel coronary artery disease might be associated with more extensive myocardial damage or ischaemia, resulting in destruction of ventricular chemo and baro receptors and alterations of afferent parasympathetic transmission.

BAROREFLEX SENSITIVITY AND HEART RATE VARIABILITY

The lack of correlation between temporal measures of heart rate variability and baroreflex sensitivity is not unexpected as it has been suggested that baroreflex sensitivity and heart rate variability may examine different but complementary components of the parasympathetic nervous system. Consequently the prognostic value of these tests may differ considerably. In this study, baroreflex sensitivity was significantly reduced only in those patients with arrhythmic events, whereas the heart rate variability index was significantly reduced when either arrhythmic events or cardiac mortality was analysed. Bigger *et al* have studied the relation between baroreflex sensitivity and frequency domain analysis of heart rate variability in 32 patients after infarction. They found only a moderate correlation between baroreflex sensitivity and the high frequency component of the normal RR interval power spectrum but they concluded that the association was not strong enough to make baroreflex sensitivity testing redundant.[30] It should be stressed that reduced heart rate variability does not necessarily predict reduced baroreflex sensitivity and important information may be obtained from both tests. Temporal measures of heart rate variability may represent primary tonic vagal activity whereas baroreflex sensitivity represents the maximum response of the autonomic nervous system to barostress, which may be of particular importance in protecting myocardial electrical stability.[31] This finding may account for the disparity between heart rate variability and baroreflex sensitivity in our study. The pNN50 index has been reported to be the most sensitive heart rate variability measure of parasympathetic tone[32] and might have been expected to correlate with baroreflex sensitivity. Although it did not, there was a significant correlation between the pNN50 and the maximum change in RR intervals on baroreflex sensitivity testing.

BAROREFLEX SENSITIVITY AND ARRHYTHMIC RISK

The striking feature of our study is that baroreflex sensitivity testing was a very strong marker of arrhythmic risk. Patients with depressed baroreflex sensitivity (< 3·0 ms/mm Hg) had a relative risk for arrhythmic events during follow up of 23·1, superior to any other variable including the different measures of heart rate variability and conventional investigations. In particular baroreflex sensitivity was a much better indicator of arrhythmic propensity than impaired left ventricular function (relative risk 10·4) or frequent ventricular extrasystoles (relative risk 20·6). It is of note that baroreflex sensitivity was reduced in patients with frequent ventricular extrasystoles and repetitive forms on long term electrocardiographic recordings, markers of arrhythmic potential.

It is well recognised that the electrical stability of the myocardium is influenced by both divisions of the autonomic nervous system. Sympathetic or adrenergic stimulation is known to reduce ventricular refractoriness and fibrillation threshold and to increase the propensity to arrhythmias; it may also produce afterdepolarisations and triggered activity.[33 34] Vagal stimulation opposes these effects, prolonging ventricular refractoriness and reducing the effects of adrenergic stimulation.[35] Indeed, the inhibitory effects of vagal stimulation are more pronounced in the setting of adrenergic stimulation than as an isolated stimulus.[36] Normally, afferent nerve transmission from the arterial baroreceptors to the higher centres results in inhibition of the sympathetic outflow while concomitantly increasing efferent parasympathetic activity. Myocardial infarction may interfere with this mechanism in several ways. Denervation of the myocardium as a consequence of infarction may produce several effects: areas of myocardium may become supersensitive to catecholamines and the de-

Table 4 Summary of investigations in patients with arrhythmic events

Patient No	*Event*	*BRS (ms/mm Hg)*	*HRV SD RR (ms)*	*HRV index (ms)*	*LVEF%*	*ETT*	*SAECG*	*VE10*	*CAD*
1	VT	1·42	32	17·0	22	+	–	+	1
2	VT	2·32	35	8·6	45	+	+	+	3
3	VT	0·6	34	9·2	39	+	+	+	2
4	SD	4·6	67	17·3	47	+	+	+	1
5	SD	3·2	46	12·4	39	–	–	–	2
6	SD	0·3	68	18·7	33	+	+	+	3
7	SD	2·4	90	29·9	26	+	–	+	1
8	SD	0·5	31	11·0	20	+	+	+	1
9	VT	0·7	45	16·5	35	–	+	–	1
10	VT	1·1	77	27·0	27	+	+	+	3

BRS, baroreflex sensitivity; HRV, heart rate variability; LVEF%, left ventricular ejection fraction; ETT, exercise tolerance test; SAECG, signal averaged elctrocardiogram; VE10, greater than 10 extrasystoles in any one hour on long term electrocardiographic recording; CAD, number of diseased arteries; VT, representation with sustained ventricular arrhythmias; SD, sudden or arrhythmic death; +, positive; –, negative.

struction of afferent neural fibres and receptors may result in the impairment and loss of protective cardiac reflexes producing a tendency towards electrical instability.[37 38] Lowered baroreflex sensitivity can lead to increased sympathetic drive with decreased vagal activity, a situation encouraging the genesis of ventricular arrhythmias particularly in the setting of myocardial ischaemia.

Table 4 gives details of each arrhythmic event and shows that conventional risk factors would have failed to identify several cases. Not all patients had impaired ventricular function or multivessel disease and markers of electrical instability were absent in several cases. Autonomic function and in particular baroreflex sensitivity was considerably reduced in all patients. Although patient 4 had a baroreflex sensitivity of 4·6 ms/mm Hg, this was still well below the group mean and would be considered low for a 36 year old man. Whether baroreflex sensitivity is an independent predictor of arrhythmic propensity will require further investigation involving a larger group of patients. When adjusted for age and ventricular function baroreflex sensitivity was still significantly lower in the arrhythmic group, however. It is hoped that a large multicentre trial (Autonomic Tone and Reflexes After Myocardial Infarction, ATRAMI) will answer these questions.

Conclusion

This paper draws attention to the association between autonomic tone, arrhythmic risk and death after infarction. Baroreflex sensitivity assessment is safe and can be performed soon after infarction. It provides different but complimentary data to heart rate variability and in our present study the prognostic value of baroreflex sensitivity appears to be independent of the effects of age and left ventricular function. Its precise value as an independent predictor of arrhythmic events and its relation to other prognostic variables will require further investigation. Such studies, including the ATRAMI trial, are in progress.

1 Theroux P, Walters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;**301**: 341–5.

2 Marcus FT, Cobb LA, Edwards JE, *et al*, and The Multicenter Post Infarction Group. Mechanism of death and prevalence of myocardial ischaemia symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol* 1988;**61**:8–15.

3 Scheultz RA, Strauss HW, Pitt B. Sudden cardiac death in the year following myocardial infarction. Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. *Am J Med* 1977;**62**:192–9.

4 Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, and The Multicenter Post Infarction Research Group. The relationship among ventricular arrhythmias, left ventricular dysfunction and mortality in the two years after myocardial infarction. *Circulation* 1984;**69**:250–8.

5 Gomes JA, Winters SL, Martinson M, *et al*. The prognostic significance of quantitative signal averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: a prospective study. *J Am Coll Cardiol* 1989;**13**:377–84.

6 Cripps TR, Bennett ED, Camm AJ, Ward DE. Inducibility of sustained monomorphic ventricular tachycardia as a prognostic indicator of survival in recovering post-infarction patients. *J Am Coll Cardiol* 1989;**14**:289–96.

7 Leclercq JF, Maisonblanche P, Cauchemez B, Coumel P. Respective role of sympathetic tone and of cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holter monitoring. *Eur Heart J* 1988;**9**:1276–83.

8 Corr PB, Yamada KA, Witkowski FX. Mechanisms controlling cardiac autonomic function and their relationship to arrhythmogenesis. In: Fozzard HA, Haber E, Jennings RB, Katz AM, eds. *The heart and cardiovascular system.* New York: Raven, 1986:1343–404.

9 Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med* 1976;**294**:1165–70.

10 Webb SW, Adgey AAJ, Pandtridge JF. Autonomic disturbance at onset of acute myocardial infarction. *BMJ* 1972;**3**:89–92.

11 Rothschild M, Rothschild R, Pfeifer M. Temporary decrease in cardiac parasympathetic tone after acute myocardial infarction. *Am J Cardiol* 1988;**62**:637–9.

12 Schwartz PJ, Zara A, Pala M, *et al*. Baroreflex sensitivity and its evolution during the first year after myocardial infarction. *J Am Coll Cardiol* 1988;**12**:629–36.

13 Farrell TG, Paul V, Cripps TR, *et al*. Baroreflex sensitivity and electrophysiological correlates in post infarction patients. *Circulation* 1991;**83**:945–52.

14 Schwartz PJ, Vanoli E, Stramba-Badiale, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988;**78**:969–79.

15 Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. *Circ Res* 1987;**61**:429–35.

16 Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, and The Multicenter Post Infarction Research Group. Heart rate variability: a predictor of mortality following acute myocardial infarction. *Am J Cardiol* 1987;**59**:256–62.

17 Farrell TG, Bashir Y, Cripps T, Malik M, Bennett ED, Camm AJ. Accurate risk stratification for arrhythmic events based only on Holter variables in post infarction patients [abstract]. *Circulation* 1990;**82**(suppl 111):551.

18 La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates and cardiovascular mortality amongst patients with a first myocardial infarction. A prospective study. *Circulation* 1988;**78**: 816–24.

19 Greene HL, Richardson DW, Barker AH, *et al*, and The Cardiac Arrhythmia Pilot Study Investigators. Classification of deaths after myocardial infarction as arrhythmic or non-arrhythmic. *Am J Cardiol* 1989;**63**:1–6.

20 Smyth SH, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: a quantitative method of analysing baroreflex sensitivity. *Circ Res* 1969; **24**:109–21.

21 Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: selection of optimal processing techniques. *Eur Heart J* 1989;**10**:1060–74.

22 Simpson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 1981;**64**:235–42.

23 Eckberg DL. Baroreflex inhibition of the human sinus node: importance of stimulus intensity, duration and rate of

pressor change. *J Physiol (Lond)* 1977;269:561–77.

24 Guo GB, Thames MD, Abboud FM. Differential baroreflex control of heart rate and vascular resistance in rabbits. *Circ Res* 1982;50:554–65.

25 Eckberg DL, Drabinski M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877–83.

26 La Rovere MT, Mortara A, Ghio S, Specchia G, Schwartz PJ. Baroreflex sensitivity and left ventricular function in post myocardial infarction patients [abstract]. *Circulation* 1987;76(suppl V):59.

27 Thames MD, Klopfenstein HS, Abboud FM, Mark AL, Walker JL. Preferential distribution of inhibitory cardiac receptors with vagal afferent to the inferoposterior wall of the left ventricle activated during coronary occlusion in the dog. *Circ Res* 1978;45:512–9.

28 Barber MJ, Mueller TM, Davis BG, Gill RM, Zipes DP. Interruption of sympathetic and vagal mediated afferent responses by transmural infarction. *Circulation* 1985; 72:623–31.

29 Hayano J, Sakakibara Y, Yamada M, *et al.* Decreased magnitude of heart rate spectral components in coronary artery disease. *Circulation* 1990;81:1217–24.

30 Bigger JT Jr, La Rovere MT, Steinman RC, *et al.* Comparison of baroreflex sensitivity and heart period variability after myocardial infarction. *J Am Coll Cardiol* 1989;14:1511–8.

31 Myers RW, Pearlman AS, Hyman RM, *et al.* Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial infarction. *Circulation* 1974;49:943–7.

32 Ewing DJ, Neilson JMM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *Br Heart J* 1984;52:396–402.

33 Wit AL, Cranfield PF. Triggered and automatic activity in the canine coronary sinus. *Circ Res* 1977;41:435–45.

34 Verrier RL, Lown B. Sympathetic-parasympathetic interactions and ventricular electrical stability. In: Schwartz PJ, Brown AM, Malliani A, Zanchetti A, eds. *Neural mechanisms in cardiac arrhythmias.* New York: Raven Press, 1978:75–85.

35 Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischaemic myocardium: influences of heart rate and vagal stimulation. *Circulation* 1973;47: 291–8.

36 Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res* 1971;29:437–45.

37 Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. *Circulation* 1987;75:877–87.

38 Waxman MB, Wald R. Terminationn of ventricular tachycardia by an increase in cardiac vagal drive. *Circulation* 1977;56:385–91.

Br Heart J 1992;67:138–43

Immediate and long term results of percutaneous coronary angioplasty in patients aged 70 and over

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Abstract

Objective—To study the immediate and long term clinical success of percutaneous transluminal coronary balloon angioplasty in patients over 70 years old.

Design—Patients undergoing percutaneous transluminal angioplasty were prospectively entered in a specially designed database. The clinical and angiographic data of all patients over 70 were reviewed. Follow up data were collected by interview during outpatient visits, by questionnaire, or through the referring physician.

Setting—A tertiary referral cardiac centre.

Patients—166 patients over 70 (median 73, range 70–84) underwent coronary angioplasty because of unstable angina (81 patients), stable angina (76 patients), or acute myocardial infarction (nine patients).

Results—The initial clinical success rate was 86% (142 of 166 patients). A major procedural complication occurred in 10 patients (6%): four patients (2%) died, six patients (4%) underwent emergency bypass surgery, and five patients (3%) sustained an acute myocardial infarction. In 14 patients (8%) coronary angioplasty did not significantly reduce the diameter stenosis but there were no associated complications. A total of 226 lesions were attempted. The initial angiographic success rate was 192 out of 226 lesions (85%). The median follow up was 21 (range 0·5–66) months. Sixteen patients (10%) died during follow up, eight patients (5%) sustained a non-fatal myocardial infarction, 21 patients (13%) underwent a second or third balloon dilatation, and 17 patients (10%) underwent elective bypass surgery. Of the 146 survivors, 99 patients (68%) had sustained clinical improvement. The estimated survival at four years (Kaplan-Meier method) was 89 (SD 4)%. The event free survival at four years for the total study population was 61 (8)%. Multivariate logistic regression analysis showed that the extent of vessel disease was the only independent predictive factor for event free survival: the event free survival rate was 81 (10)% at four years for patients with single vessel disease, compared with 45 (12)% for patients with multivessel disease.

Conclusions—Coronary angioplasty in patients over 70 was a safe and effective treatment for obstructive coronary artery disease. The extent of vessel disease, and not the completeness of revascularisation, was the only independent predictive factor for event free survival.

An increasing proportion of the population consists of elderly people.[1] Because the incidence of coronary heart disease increases with age, it is not surprising that more and more elderly patients are referred for coronary angiography.[2] As a consequence, the numbers of coronary angioplasty procedures and coronary artery bypass operations in this subgroup of the population will increase as well. Coronary artery bypass grafting in geriatric patients is associated with increased morbidity and mortality.[3-5] Coronary angioplasty is a less invasive procedure and may be an attractive non-surgical alternative. In general, the elderly patient has more advanced coronary artery disease and lesions that are more calcified. Sometimes the coronary arteries are rigid and tortuous.[5-7] These morphological and angiographic characteristics make coronary angioplasty technically more difficult to perform and may lead to less satisfactory results.

We examined the safety and efficacy of coronary angioplasty in elderly patients in terms of the initial angiographic and clinical success rate and the long term results.

Patients and methods

Between January 1983 and September 1988 coronary angioplasty was performed in 166 patients over 70 years old. They represent 8% of the total coronary angioplasty population (n = 2002) during the same period. Table 1 shows the clinical and angiographic character-

Table 1 Clinical and angiographic characteristics

Characteristic	*Patients n (%)*
Total number of patients	166
Age (yr):	
Median	73
Range	(70–84)
Male	86 (52)
Previous myocardial infarction	65 (39)
Previous coronary artery bypass surgery	17 (10)
Vessel disease:	
Single	87 (52)
Double	52 (31)
Triple	27 (16)
Ejection fraction (%):	
Median	59
Range	(18–77)

istics. The indication for coronary angioplasty was unstable angina in 81 patients (49%), stable angina in 76 patients (46%), and acute myocardial infarction in nine patients (5%). Until 1988, patients with an acute myocardial infarction were treated with intravenous and intracoronary streptokinase followed by angioplasty if the residual stenosis was >50%. Unstable angina pectoris was defined as angina at rest associated with reversible changes in the ST segment or T wave without evidence of ensuing myocardial necrosis as assessed by increased cardiac enzyme activity or the development of new Q waves. Seven patients underwent coronary angioplasty of a stenosis in the left main stem. Two patients had a left main stem artery protected by the presence of a patent bypass graft, one patient was admitted because of an acute myocardial infarction complicated by cardiogenic shock, and four patients were regarded as high risk surgical cases because of severe peripheral vascular disease, renal insufficiency, obstructive lung disease, or previous stroke.

The global ejection fraction was calculated from a single plane left ventricular angiogram in the 30° right anterior oblique view according to Simpson's rule.

CORONARY ARTERIOGRAPHY

Coronary arteriography was performed via the femoral approach, with multiple views that included hemiaxial projections. The degree of stenosis was expressed as the percentage reduction in the diameter of the coronary artery lumen. A reduction in diameter of > 50% was regarded as significant. The culprit lesion in patients with acute myocardial infarction or unstable angina and multivessel disease was identified by relating the site of changes in the resting ST segment and T wave on the standard 12 lead electrocardiogram to the angiographic findings. ST-T segment changes in leads I, aVL, and V1–6 were related to lesion(s) of the left anterior descending coronary artery. Changes in leads II, III, and aVF were related to lesion(s) of the right or circumflex coronary artery. A total occlusion was defined as the absence of anterograde flow, and a functionally occluded artery was defined as the incomplete opacification of the distal vessel.

CORONARY ANGIOPLASTY

Coronary angioplasty was performed with preformed guiding catheters, steerable dilating balloon catheters, and a pneumatic inflation device. Before the dilatation, a 7 French pacing electrode was positioned in the right atrium, and 10 000 units of heparin and 250 mg of aspirin were administered intravenously. Intracoronary isosorbide dinitrate was given to prevent coronary spasm. Four electrocardiographic leads and the aortic pressure were monitored continuously. Balloon inflation started at a pressure of 2 atm and was increased to 12 atm if necessary. The inflation was stopped when electrocardiographic changes, a considerable drop in blood pressure, or pain developed. The dilatation was repeated until there was a significant reduction of the diameter stenosis. Angioplasty was considered to be angiographically successful when obstruction of the luminal diameter was reduced to < 50%. A dissection was defined as the presence of intimal damage producing an intraluminal defect on the coronary angiogram, or extraluminal extravasation of contrast material, or the presence of linear luminal density or luminal staining, or a combination of these.

A clinically successful angioplasty was defined as an angiographically successful dilatation free of procedure related complications that led to acute myocardial infarction, emergency bypass surgery, or death. A periprocedural infarction was determined by the development of new Q waves (0·04 s) or an increase in serum cardiac enzyme activities of more than twice the upper limit of normal. A perioperative myocardial infarction was defined by the development of new Q waves.

Dilatation within two or more major coronary arteries was described as multivessel angioplasty. Revascularisation was considered complete when all stenoses leading to a diameter reduction of > 50% were successfully dilated.

FOLLOW UP

Procedural details, including immediate complications, were prospectively recorded in a computer database at the time of balloon angioplasty. The median follow up time was 21 (range 0·5–66) months. Patients were screened for the occurrence of death, acute myocardial infarction, and recurrent angina necessitating repeat angioplasty or bypass surgery. Clinical follow up information was obtained at interview during outpatient visits, by questionnaire, or through the referring physician. Information was complete for all patients. Patient survival curves and event free plots were constructed by the Kaplan-Meier method.

Results

ANGIOGRAPHIC RESULTS

Percutaneous transluminal coronary angioplasty was performed in 166 patients over 70 years old. Angioplasty was attempted on a total of 226 lesions (one lesion in 117 patients (70%), two or more lesions in 49 patients (30%)). Revascularisation was complete in 101 patients (61%) and partial in 65 patients (39%).

Of the 226 stenoses, 192 were successfully

Table 2 Distribution, aspect, and angiographic success of lesions on which angioplasty was attempted

	No (%)	*Success rate (%)*
Total number of lesions	226	192 (85)
Site:		
LAD	128 (57)	114 (89)
CX	49 (22)	40 (82)
RCA	38 (17)	18 (74)
Left main stem	7 (3)	6 (86)
Venous graft	4 (2)	4 (100)
Functionally occluded artery	11 (5)	9 (82)
Totally occluded artery	15 (7)	9 (60)

LAD, left anterior descending coronary artery; CX, circumflex coronary artery; RCA, right coronary artery.

Table 3 Clinical success of coronary angioplasty and procedure related major complications in 166 patients over 70

Patients over 70	*No (%)*
Total number of patients	166
Clinical success	142 (86)
Unsuccessful angioplasty without complications	14 (8)
Unsuccessful angioplasty with complications:	10 (6)
Death	4 (2)
AMI	5 (3)
CABG	6 (4)

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting.

Table 4 Clinical success of coronary angioplasty according to indication in 166 patients aged $\geqslant 70$

Indication	*No of patients in which angioplasty was attempted*	*Success (%)*
UAP	81	73 (90)
AP	76	61 (80)
AMI	9	8 (81)

UAP, unstable angina pectoris; AP, stable angina pectoris; AMI, acute myocardial infarction.

dilated. The overall primary angiographic success rate was 85%. Table 2 shows the distribution of the lesions and the success rate per lesion. The lesion could not be crossed in four patients (2%). In three of these the attempt to cross the lesion with the guide wire resulted in dissection and subsequent occlusion. These three patients died of acute myocardial infarction complicated by cardiogenic shock. The fourth patient was referred for emergency bypass surgery. Abrupt closure of the artery immediately after attempted dilatation occurred in 10 patients (6%). In three patients a major coronary dissection was found, but in the other seven patients the mechanism of the acute occlusion was uncertain. They were all successfully redilated. A dissection was seen in another 14 patients (8%). One patient died, one sustained an acute myocardial infarction, and three underwent emergency bypass surgery.

CLINICAL RESULTS

The primary clinical success rate for the total study population was 86% (table 3). In 14 patients (8%) the angioplasty did not significantly reduced the diameter stenosis, but there were no complications. Ten patients (6%) had a major procedure related complication. Acute myocardial infarction was seen in four patients, of whom one died and two were referred for emergency bypass surgery. Another four patients underwent urgent bypass surgery, of these one patient died of a perioperative myocardial infarction. Two other patients had ventricular fibrillation during angioplasty and subsequently died. A total of 15 complications occurred in 10 patients (6%). Table 4 shows the clinical success according to indication. One patient sustained a transient ischaemic cerebrovascular accident and another patient required surgical repair of a pseudoaneurysm of the right femoral artery. Single vessel and multivessel angioplasty were performed in 146 (88%) and 20 patients (12%) respectively. Of the 146 patients who underwent single vessel angioplasty, one lesion was attempted in 117 patients (80%), and two or more lesions were attempted within the same coronary artery in 29 patients (20%). A total of 12 events occurred in eight patients undergoing single vessel angioplasty and three events occurred in two patients undergoing multivessel angioplasty (table 5).

Table 5 Complication rate of single vessel and multivessel angioplasty in patients aged $\geqslant 70$

	Single vessel (%)	*Multivessel (%)*
Total number of patients	146	20
Death	3 (2·1)	1 (5)
AMI	4 (2·7)	1 (5)
CABG	5 (3·4)	1 (5)

AMI, procedure related acute myocardial infarction; CABG, emergency bypass surgery.

FOLLOW UP

Table 6 lists the data from the clinical follow up after successful and unsuccessful angioplasty. There were 16 deaths (10%) of which 10 were cardiac and six non-cardiac. Eight patients (5%) sustained a late non-fatal acute myocardial infarction. Symptoms recurred in 44 patients (27%). Six patients (4%) were treated medically. Repeat angioplasty was carried out on 21 patients (13%) (the same lesion in 13 patients and a newly acquired lesion in eight patients), of whom one died and four underwent a third uncomplicated coronary angioplasty. Seventeen patients (10%) underwent elective bypass surgery; one of these patients had an uncomplicated perioperative myocardial infarction. Table 6 shows the interval between the first coronary angioplasty and the cardiac events during follow up.

The mean (SD) estimated survival at four years from the first angioplasty for the entire study population was 89 (4)% (fig 1). The event free survival at four years (free of myocardial infarction, bypass surgery, and repeat angioplasty) was 61 (8)% (fig 1). To determine independent predictors for event free survival, multivariate logistic stepwise regression analysis was performed. Several variables were selected—namely, age $>$ 75 years, sex, previous myocardial infarction, previous bypass surgery, ejection fraction $<$ 55%, stable *v* unstable angina, completeness of revascularisation, and extent of vessel disease (single *v* multivessel disease). The extent of vessel disease was the only independent predictive factor. The probability of sustaining a cardiac event was 4·7 fold higher (95% confidence interval 2·3–9·3) in patients with multivessel

Table 6 Major cardiac events during follow up of 166 patients aged $\geqslant 70$ who underwent coronary angioplasty

Event	*Group 1 (%)*	*Group 2 (%)*	*Group 3 (%)*	*Total (%)*	*Interval (months) Median (range)*
	142 (86)	14 (8)	10 (6)	166	
Death	13	3	—	16 (10)	9 (0·5–39)
AMI	3	4	1	8 (5)	3 (2–13)
Re PTCA	21	—	—	21 (13)	5 (1–32)
CABG	12	2	3	17 (10)	6 (1–35)

Group 1, successful coronary angioplasty; group 2, unsuccessful coronary angioplasty without complications; group 3, unsuccessful coronary angioplasty with major complications; AMI, acute myocardial infarction; Re PTCA, repeat coronary angioplasty; CABG, coronary artery bypass grafting.

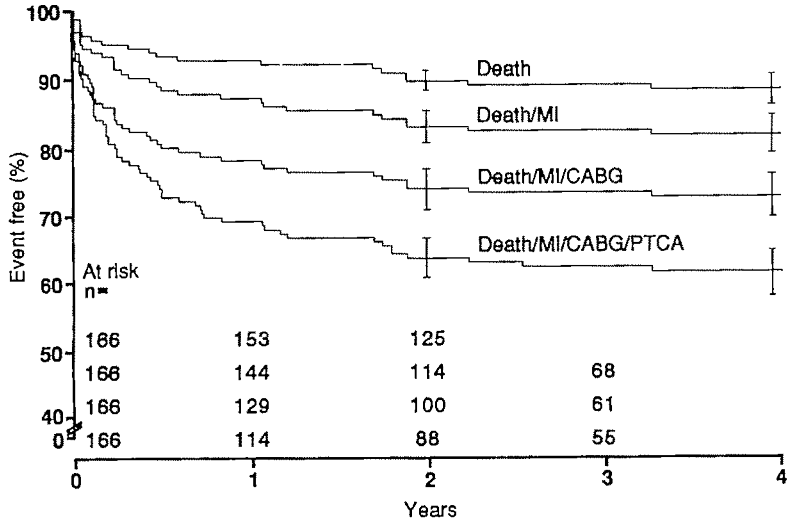

Figure 1 Overall long term cumulative survival and event free survival curves after balloon angioplasty according to the Kaplan-Meier method for patients aged ≥ 70. Vertical bars denote the 95% confidence intervals. For abbreviations see table 6.

disease compared with those with single vessel disease. Event free survival at four years was 81 (10)% in patients with single vessel disease compared with 45 (12)% in patients with multivessel disease (fig 2).

At the end of follow up 146 patients (88%) were still alive. Ninety nine patients (68%) were improved clinically. This was associated with an appreciable reduction in antianginal therapy. Before angioplasty, 136 patients were being treated with β blockers, 107 with nitrates, and 145 patients with calcium antagonists. At the end of follow up only 41 patients still took β blockers (a reduction of 70%), 18 still took nitrates (a reduction of 83%), and 106 patients took calcium antagonists (a reduction of 27%).

Discussion

As the population of developed countries ages the number of elderly patients referred for diagnostic and therapeutic cardiac catheterisations continues to increase. From January 1983 to August 1988, 2002 coronary angioplasties were performed in our hospital and the percentage of patients over 70 who underwent balloon angioplasty increased from 7% to 15%. In the United States one third of the cardiac catheterisations and one third of the coronary artery bypass operations are performed on elderly patients.[8,9] Coronary artery bypass grafting in the elderly is an effective method of myocardial revascularisation, providing symptomatic relief and good long term results.[10–12] Cardiac surgery in the geriatric patient is, however, associated with increased morbidity and mortality.[3,12,13] In view of this high operative risk, coronary angioplasty is particularly attractive as a less invasive alternative. It offers the potential for myocardial revascularisation with certain advantages over bypass grafting such as the avoidance of a thoracotomy, shorter time in hospital, and lower costs.[6,7,14] A lower success rate may be expected for balloon angioplasty performed in the elederly. As well as the increased procedural mortality known to occur in patients over 70, other clinical variables noted more often in the elderly, such as depressed left ventricular function and left main and three vessel coronary artery disease, increase the risk associated with balloon angioplasty.[15,16] Elderly patients also have more tortuous coronary arteries and more calcified lesions, which create troublesome angles and bends to negotiate.[5–7] Our data from this study indicate that coronary angioplasty can be performed with a high initial success rate and an acceptable incidence of complications in patients over 70. These data accord with previous reports (table 7). Three earlier studies compared the primary success rate and incidence of complications of balloon angioplasty between patients younger than and older than 65.[14,17,18] Only the National Heart, Lung and Blood Institute (NHLBI) percutaneous transluminal coronary angioplasty registry showed a significantly lower initial success rate and a higher mortality in the elderly patients.[14] The population of the NHLBI study, however, differed from the other studies in that the data were collected from many institutions during the period 1977 to 1981. The higher success rate reported in the other studies can in part be explained by improved angioplasty equipment and increased operator experience. Also in this study and in other reports no patients sustained an irreversible cerebrovascular accident whereas 2·7–7·5% of patients in surgical series did.[6,11,21]

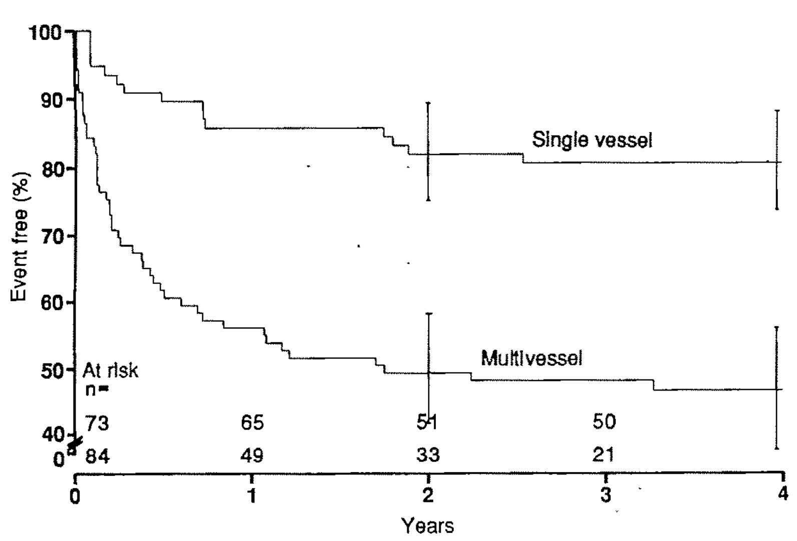

Figure 2 Event free survival after balloon angioplasty according to the Kaplan-Meier method for patients aged ≥ 70 with single or multivessel disease. Vertical bars are 95% confidence intervals.

Though it is difficult to compare different studies, especially when there is selection bias, there is a striking similarity between the overall and the event free survival rates in our patient group and those reported by others.[19–21] Also, the estimated survival at four years of 89 (4)% compares favourably with the survival rate for elderly patients who undergo bypass surgery.[11,24,25] The importance of complete revascularisation after bypass surgery is well documented.[26,27] It has been shown that complete revascularisation is associated with improved long term survival and freedom from late cardiac events.[28–30] Variables other than the

Table 7 Reported angiographic and clinical success rate and complications after balloon angioplasty in elderly patients

					Complications (%)		
Author		*Number of patients*	*Angiographic success (%)*	*Clinical success (%)*	*Death*	*AMI*	*CABG*
			Patients ≥ 65 years				
Mock *et al*[14]	1984	370	—	53	2·2	5·6	6·8
Jones *et al*[17]	1986	159	84	81	0·0	3·1	5·7
Raizner *et al*[18]	1986	119	81	—	0·8	2·5	4·1
Bedotto *et al*[19]	1991	1373	96	—	1·6	1·4	0·8
			Patients ≥ 70 years				
Dorros and Janke[6]	1986	109	89	83	1·8	2·8	0·9
Holt *et al*[20]	1988	54*	—	80	0·0	4·0	6·0
Simpfendorfer *et al*[21]	1988	124†	—	90	0·0	0·8	4·0
		212*	—	93	0·9	0·9	2·8
			Patients ≥ 80 years				
Kern *et al*[22]	1988	21	78	67	19·0	—	1·4
Rich *et al*[23]	1990	22	89	—	0·0	14·0	0·0

AMI, acute myocardial infarction; CABG, emergency bypass surgery. *Only patients with unstable angina; †only patients with stable angina.

degree of revascularisation, however, may influence the long term outcome. Moreover, there may be substantial differences in baseline characteristics between patients with complete and incomplete revascularisation.[31 32] In this respect, conclusions about long term outcome based only on the degree of revascularisation may be misleading. It has been shown that after adjustment of such baseline differences in patients with multivessel disease undergoing balloon angioplasty, the completeness of revascularisation has no independent predictive value for event free survival.[31 32] The data from this study indicate that the extent of vessel disease and not the degree of revascularisation is the only independent predictor for event free suurvival.

STUDY LIMITATIONS

The group of patients we describe is clearly a selected population. Patients were not randomised to either angioplasty or bypass surgery. Therefore, no attempt was made to compare the results of balloon angioplasty with those achieved by bypass surgery. Published data on angioplasty and coronary artery bypass surgery, however, provide some insight into the benefit:risk ratio when choosing which treatment should be used for the geriatric patients. Angioplasty can only truly be compared with bypass surgery in randomised trials, such as are currently under way in Europe and The United States.

In conclusion, coronary angioplasty can be performed safely and effectively in the elderly. Given the favourable long term results this procedure should be considered as a therapeutic alternative to coronary bypass surgery in this group of patients.

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1 Simons LA. Epidemiologic considerations in cardiovascular diseases in the elderly: international comparisons and trends. *Am J Cardiol* 1989;63:5H–8H.
2 Kennedy RD, Andrews GR, Caird FI. Ischaemic heart disease in the elderly. *Br Heart J* 1977;39:1121–7.
3 Knapp WS, Douglas JS, Craver JM, King SB III, Bone DK, Bradford JM, *et al.* Efficacy of coronary artery bypass grafting in elderly patients with coronary artery disease. *Am J Cardiol* 1981;47:923–30.
4 Faro RS, Golden MD, Javid H, Serry C, DeLaria GA, Monson D, *et al.* Coronary revascularisation in septuagenarians. *J Thorac Cardiovasc Surg* 1983;86:616–20.
5 Kennedy JW, Kaider GC, Fisher LD, Fritz JK, Myers W, Mudd G, *et al.* Clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery. *Circulation* 1981;63:793–802.
6 Dorros G, Janke L. Percutaneous transluminal coronary angioploasty in patients over the age of 70 years. *Cathet Cardiovasc Diagn* 1986;12:223–9.
7 Kelly ME, Taylor GJ, Moses HW, Mikell FL, Dove JT, Batchelder JE, *et al.* Comparative cost of myocardial revascularisation: percutaneous transluminal angioplasty and coronary artery bypass surgery. *J Am Coll Cardiol* 1985;5:16–20.
8 Kashyap M. Cardiovascular disease in the elderly: current considerations. *Am J Cardiol* 1989;63:3H–4H.
9 Stason WB, Sanders CA, Smith HC. Cardiovascular care of the elderly: economic considerations. *J Am Coll Cardiol* 1987;10:18A–21A.
10 Elayda MS, Hall RJ, Gray AG, Mathur VS, Cooley DA. Coronary revascularisation in the elderly patient. *J Am Coll Cardiol* 1984;3:1398–402.
11 Horneffer PJ, Gardner TJ, Manolio TA, Hoff SJ, Rykier MF, Pearson TA, *et al.* The effect of age on outcome after coronary bypass surgery. *Circulation* 1987;76(suppl V): V6–12.
12 Acinapura AJ, Rose DM, Cunningham JN, Jacobowitz IJ, Kramer MD, Zisbrod Z. Coronary artery bypass in septuagenarians. Analysis of mortality and morbidity. *Circulation* 1988;78(suppl 1):179–84.
13 Hochberg MS, Levine FH, Daggett WM, Akins CW, Austen G, Buckley MJ. Isolated coronary artery bypass grafting in patients seventy years of age and older. *J Thorac Cardiovasc Surg* 1982;84:219–23.
14 Mock MB, Holmes DR, Vlietstra RE, Gersh BJ, Detre KM, Kelsey SF, *et al.* Percutaneous transluminal coronary angioplasty (PTCA) in the elderly patient: experience in the National Heart, Lung and Blood Institute PTCA Registry. *Am J Cardiol* 1984;53:89C–91C.
15 Hartler GO, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV. "High risk" percutaneous transluminal coronary angioplasty. *Am J cardiol* 1988;61:33G–7G.
16 O'Keefe JH, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Lignon RW, *et al.* Multivessel coronary angioplasty from 1980 to 1989: procedural results and long-term outcome. *J Am Coll Cardiol* 1990;16:1097–102.
17 Jones EL, Abi-Monsour P, Gruntzig AR. Coronary artery bypass surgery and percutaneous transluminal coronary angioplasty in the elderly. *Cardiology* 1986;73:223–34.
18 Raizner AE, Hust RG, Lewis JM, Winters WL, Batty JW, Roberts R. Transluminal coronary angioplasty in the elderly. *Am J Cardiol* 1986;57:29–32.
19 Bedotto JB, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Shimshak TM, *et al.* Results of multivessel percutaneous transluminal coronary angioplasty in persons aged 65 years and older. *Am J Cardiol* 1991;67: 1051–5.
20 Holt GW, Sugrue DD, Breshnahan JF, Vliestra RE, Breshnahan DR, Reeder GS, *et al.* Results of percutaneous transluminal coronary angioplasty for unstable angina in patients 70 years of age and older. *Am J Cardiol* 1988;61:994–7.
21 Simpfendorfer C, Raymond R, Schraider J, Badhwar K, Dorosti K, Franco I, *et al.* Early and long-term results of percutaneous transluminal coronary angioplasty in patients 70 years of age and older with angina pectoris. *Am J Cardiol* 1988;62:959–61.
22 Kern MJ, Deligonoul U, Galan K, Zelman R, Gabliani G. Bell ST, *et al.* Percutaneous transluminal coronary angioplasty in octogenarians. *Am J Cardiol* 1988;61:457–8.
23 Rich JJ, Crispino CM, Saporito JJ, Domat I, Cooper WM. Percutaneous transluminal coronary angioplasty in patients 80 years of age and older. *Am J Cardiol* 1990; 65:675–6.
24 Gersh BJ, Kronmal RA, Schaff HV, Frye RL, Ryan TJ, Mock MB, *et al.* Comparison of coronary artery bypass surgery and medical therapy in patients 65 years of age or older. *N Engl J Med* 1985;313:217–24.

25 Horvath KA, DiSesa VJ, Peigh PS, Couper GS, Collins JJ, Cohn LH. Favourable results of coronary artery bypass grafting in patients older than 75 years. *J Thorac Cardiovasc Surg* 1990;99:92–6.

26 Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR, Riechwald N. Importance of complete revascularisation in performance of coronary bypass operation. *Am J Cardiol* 1983;51:7–12.

27 Lawrie GM, Morris GC, Silvers A, Wagner WF, Baron AE, Beltangady SS, *et al.* The influence of residual disease after coronary artery bypass on the 5-year survival rate of 1274 men with coronary artery disease. *Circulation* 1982; 66:717–23.

28 Lavee J, Rath S, Tran-Quang-Hoe. Does complete revascularisation by the conventional method truly provide the best possible results? Analysis of results and comparison with revascularisation of infarct-prone segments (systematic segmental myocardial revascularisation): the Sheba Study. *J Thorac Cardiovasc Surg* 1986;92:279–90.

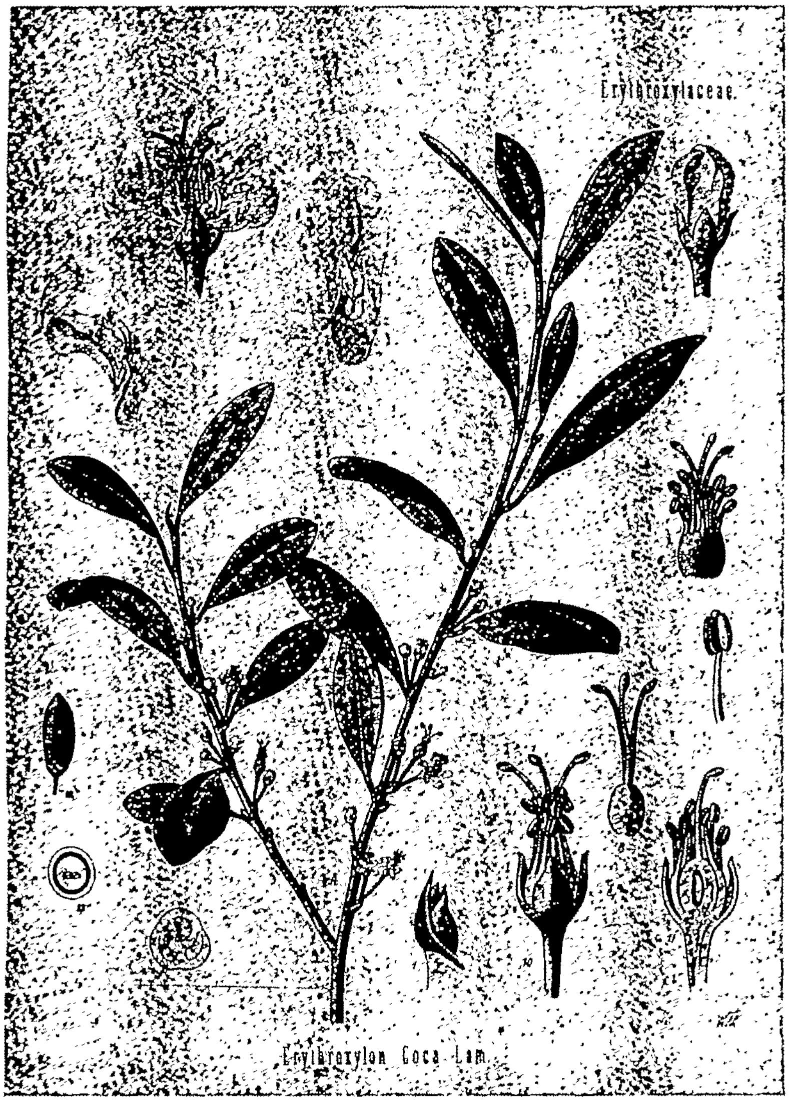
29 Cukingnan RA, Carey JS, Witting JH, Brown BG. Influence of complete coronary revascularisation on relief on angina. *J Thorac Cardiovasc Surg* 1980;79:188–93.

30 Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR, Riechwald N. Importance of complete revascularisation in performance of the coronary bypass operation. *Am J Cardiol* 1983;51:7–12.

31 Reeder GS, Holmes DR, Detre K, Costigan T, Kelsey SF. Degree of revascularisation in patients with multivessel coronary disease: a report from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty registry. *Circulaton* 1988;77:638–44.

32 Bell MR, Bailey KR, Reeder GS, Lapeyre AC III, Holmes DR. Percutaneous transluminal angioplasty in patients with multivessel coronary disease: how important is complete revascularisation for cardiac event-free survival? *J Am Coll Cardiol* 1990;16:553–62.

PLANTS IN CARDIOLOGY



Royal Botanic Gardens Kew

Erythroxylum coca Lam. Kohler F E. *Medizinal-Pflanzen, Atlas.* Gera untermhaus: E Kohler, 1887, plate 76.

Procaine and procainamide

In the early 1930s a Dr Claude S Beck was undertaking pioneer cardiac surgery at the Lakeside Hospital in Cleveland, Ohio. He was attempting to revascularise the heart in angina pectoris by putting a pedicle graft of pectoralis muscle onto the left ventricle and he was also doing pericardiectomy for constrictive pericarditis.

But arrhythmias during and after surgery presented an important problem which was investigated experimentally by Dr Frederick R Mautz. For this study he chose drugs in the cocaine group because they were readily absorbed from mucous membranes and were already known to have some effect on the myocardium. Mautz showed that in dogs procaine produced a monophasic local injury current in the epicardial electrogram and that it prevented extrasystoles when the heart was stimulated electrically (*Journal of Thoracic Surgery* 1936;5:612–28). Procaine had a quinidine-like effect but its action was short-lived owing to esterase action. Its analogue procainamide (Pronestyl) introduced in 1951 had the advantages of being enzyme resistant and active by mouth.

Cocaine was isolated in 1860 from the South American coca plant *Erythroxylum coca* (Erythroxylaceae). This shrub, the "divine plant of the Incas", grows in the eastern Andes and had been used since ancient times to induce a pleasant mental state, to combat fatigue, and increase physical endurance. This folk medicine interested Sigmund Freud and in 1884 he studied the properties of cocaine with the help of his Viennese colleague Carl Koller who was an eye surgeon. When it was found that cocaine numbed the tongue Koller at once realised its potential in ophthalmic surgery. It soon became widely used as the first ever local anaesthetic but its stimulant effect on the nervous system was unwelcome—though Sherlock Holmes took advantage of it. The less toxic synthetic compound procaine was made in 1905.

The small tropical family Erythroxylaceae has no other species with medical uses. It is interesting that two other antiarrhythmic compounds namely lignocaine and quinine are also local anaesthetics (*British Heart Journal* 1991; **65**:165 and **66**:301).

A HOLLMAN

Br Heart J 1992;67:144–9

Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease

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Abstract

***Objective*—To compare the usefulness of high dose dipyridamole stress echocardiography with dipyridamole stress electrocardiography and exercise electrocardiography for the evaluation of coronary artery disease.**

***Design*—Prospective investigation with coronary angiography as the criterion standard and blinded assessment of study data.**

***Setting*—Cardiology unit of a tertiary referral centre.**

***Subjects*—Fifty eight patients with suspected coronary disease; three of these were excluded because of poor echogenicity at baseline (test feasibility 95%). Angiography showed normal coronary arteries in 15 and coronary disease (≥70% diameter stenosis) in 40.**

***Interventions*—Cross sectional echocardiography and 12 lead electrocardiography during dipyridamole stress (up to 1 mg/kg) and exercise electrocardiography on a separate occasion. Wall motion was analysed with an 11-segment model developed at Hammersmith Hospital.**

***Main outcome measures*—Test sensitivity, specificity, and side effect data.**

***Results*—16 of 40 patients with coronary artery disease had inducible asynergy; all had multivessel disease and a tight stenosis in the vessel that supplied the abnormal segment. Exercise duration and time to 1 mm ST segment depression were significantly shorter in patients with a positive echocardiogram than in those without (both $p < 0{\cdot}01$). The sensitivity and specificity of dipyridamole stress echocardiography were 40% and 93% respectively; sensitivity improved to 60% when baseline ($n = 18$) or reversible asynergy defined an abnormal study (likelihood ratio = 9). Corresponding figures for stress electrocardiography were 38% and 80% for dipyridamole and 80% and 67% for exercise. Adverse reactions were seen in 67% of patients and included two instances of pronounced hypotension, one episode of prolonged myocardial ischaemia, and one cardiac arrest in a patient who was successfully resuscitated.**

***Conclusion*—A positive high dose dipyridamole echocardiogram predicts multivessel disease and impaired coronary reserve, but low overall sensitivity and occasionally troublesome side effects limit its clinical usefulness.**

Exercise echocardiography is an emerging technique for detection of coronary artery disease but it remains technically demanding and cannot be applied to patients unable or poorly motivated to exercise.[1] Intravenous dipyridamole stress, which provokes aberrant distribution of flow in these patients, can allow myocardial perfusion defects to be visualised on thallium scintigraphy but this approach is expensive and requires facilities for nuclear medicine.[2] Data from this centre on 21 patients with severe multivessel disease and a positive exercise electrocardiogram showed that dipyridamole provoked an echocardiographically detectable wall motion abnormality in only 11 patients.[3] It has been suggested that this limited sensitivity (52%) could be explained by the low dose of dipyridamole (0·6 mg/kg) and by the use of only the parasternal short axis projection, which made the test reliant on the adequacy of this single view for detection of transient asynergy.[4] We therefore monitored a group of patients by means of high dose dipyridamole combined with four standard echocardiographic views. The aims of this prospective study were to establish the sensitivity and specificity of high dose dipyridamole stress echocardiography in the detection of coronary disease and to compare these results with dipyridamole stress and exercise electrocardiography, and to determine the safety and side effects of dipyridamole stress echocardiography.

Patients and methods

We screened 58 patients referred for coronary angiography for suspected coronary artery disease who satisfied the study enrolment criteria. Patients with cardiac failure, unstable angina, bronchospasm, left bundle branch block, or ≥1 mm of ST segment deviation from isoelectric on the baseline electrocardiogram were excluded. Stress echocardiography was not performed on three patients because of inadequate baseline endocardial definition on transthoracic imaging (test feasibility 95%). The remaining 55 patients (41 men, mean age 55 (SD 9) (range 38–73) years) underwent dipyridamole stress echocardiography, exercise testing, and angiographic evaluation in random order (table 1). Coronary angiography showed normal coronary arteries in 15 and

Table 1 Clinical data and results of coronary angiography, exercise electrocardiography, dipyridamole stress electrocardiography, and dipyridamole stress echocardiography in 55 patients

					Dipyridamole stress echocardiography					
		Coronary angiography			*Baseline asynergy*			*New or worsening asynergy*		
Case No	*Age (yr)/sex*	*No (vessels) diseased*	*Exercise ECG*	*Dipyridamole ECG*	*+/–*	*Segment Nos*	*Nature**	*+/–*	*Segment Nos*	*Nature**
Normal subjects:										
1	43/M	None	Negative	Negative	–	–	–	–	–	–
2	62/M	None	Negative	Negative	–	–	–	–	–	–
3	42/M	None	Positive	Positive	–	–	–	–	–	–
4	42/M	None	Negative	Negative	–	–	–	–	–	–
5	43/F	None	Negative	Negative	–	–	–	–	–	–
6	62/F	None	Negative	Negative	–	–	–	–	–	–
7	43/M	None	Negative	Negative	–	–	–	–	–	–
8	47/M	None	Positive	Negative	–	–	–	–	–	–
9	43/F	None	Negative	Negative	–	–	–	–	–	–
10	55/F	None	Positive	Positive	–	–	–	+	11	Akinesis
11	50/F	None	Positive	Positive	–	–	–	–	–	–
12	53/F	None	Negative	Negative	–	–	–	–	–	–
13	71/M	None	Negative	Negative	–	–	–	–	–	–
14	54/F	None	Negative	Negative	–	–	–	–	–	–
15	61/M	None	Positive	Negative	–	–	–	–	–	–
CAD:										
1	53/M	1 LCX	Positive	Negative	–	–	–	–	–	–
2	53/M	1 LAD	Negative	Negative	–	–	–	–	–	–
3	51/M	1 LAD	Negative	Negative	–	–	–	–	–	–
4	53/F	1 LAD	Negative	Negative	–	–	–	–	–	–
5	38/F	1 LAD	Positive	Negative	–	–	–	–	–	–
6	62/M	1 RCA	Negative	Negative	–	–	–	–	–	–
7	39/F	1 RCA	Negative	Negative	–	–	–	–	–	–
8	63/M	1 RCA	Positive	Negative	+	6	Akinesis	–	–	–
9	73/M	1 LAD	Positive	Negative	–	–	–	–	–	–
10	56/M	1 LCX	Positive	Negative	–	–	–	–	–	–
11	61/F	2 LAD, LCX	Positive	Positive	+	10, 11	Akinesis	+	4	Akinesis
12	40/M	2 LAD, LCX	Negative	Positive	–	–	–	+	7, 8	Akinesis
13	68/F	2 LAD, LCX	Positive	Positive	–	–	–	+	3, 4	Hypokinesis
14	44/M	2 LAD, RCA	Positive	Positive	+	10, 11	Hypokinesis	+	6, 10	Dyskinesis
15	43/M	2 RCA, LCX	Positive	Negative	–	–	–	+	4	Akinesis
16	71/M	2 LAD, RCA	Positive	Positive	+	6	Hypokinesis	+	6	Dyskinesis
17	62/M	2 RCA, LCX	Negative	Negative	+	6	Hypokinesis	+	6	Dyskinesis
18	54/M	2 RCA, LCX	Positive	Positive	–	–	–	–	–	–
19	61/M	2 LAD, RCA	Positive	Positive	+	2, 10, 11	Akinesis	–	–	–
20	61/M	2 LAD, RCA	Positive	Positive	+	5	Hypokinesis	+	5	Dyskinesis
21	52/M	2 RCA, LCX	Positive	Negative	–	–	–	–	–	–
22	59/M	2 RCA, LCX	Positive	Negative	–	–	–	–	–	–
23	57/M	2 LAD, RCA	Positive	Negative	+	5	Hypokinesis	+	5	Dyskinesis
24	56/M	2 LAD, RCA	Positive	Negative	–	–	–	–	–	–
25	54/M	2 RCA, LCX	Positive	Negative	–	–	–	–	–	–
26	55/M	2 LAD, LCX	Positive	Negative	+	9, 10, 11	Hypokinesis	–	–	–
27	45/M	2 RCA, LCX	Positive	Negative	+	6	Hypokinesis	–	–	–
28	63/M	2 RCA, LCX	Positive	Negative	–	–	–	–	–	–
29	70/M	3	Positive	Positive	+	5	Akinesis	+	2, 10, 11	Akinesis†
30	65/M	3	Positive	Positive	–	–	–	+	6	Akinesis
31	46/F	3	Positive	Positive	–	–	–	+	4, 6	Akinesis
32	61/M	3	Positive	Positive	+	5	Akinesis	+	7, 8	Akinesis
33	50/M	3	Positive	Negative	–	–	–	+	4	Hypokinesis
34	59/M	3	Positive	Positive	+	1, 2, 9, 10, 11	Akinesis	–	–	–
35	64/F	3	Positive	Positive	+	1, 2, 9, 10, 11	Akinesis	–	–	–
36	67/M	3	Positive	Negative	+	4, 6	Hypokinesis	+	6	Dyskinesis
37	52/M	3	Positive	Positive	–	–	–	–	–	–
38	57/M	3	Positive	Negative	+	3, 5	Hypokinesis	+	3	Dyskinesis
39	71/M	3	Positive	Negative	+	3, 4	Akinesis	–	–	–
40	57/M	3	Negative	Negative	+	4, 6	Akinesis	–	–	–

*The worst grade seen is stated; † associated with transient left ventricular cavity dilatation; ECG, electrocardiography; CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

single, double, and triple vessel disease in 10, 18, and 12 patients respectively. Antianginal treatment was stopped for four half lives before both the dipyridamole and exercise stress tests and patients were asked to avoid drinks containing caffeine on the day of the dipyridamole study. All patients gave informed consent and the study was approved by the hospital ethics committee.

STUDY PROTOCOL

After collection of baseline haemodynamic, electrocardiographic and cross sectional echocardiographic data, and with the patient under continuous electrocardiographic monitoring, dipyridamole (0·6 mg/kg) was infused intravenously over five minutes. After a five minute interval a further 0·4 mg/kg was infused over five minutes. The infusion was stopped if myocardial ischaemia or notable side effects occurred, and aminophylline was given if necessary. A 12 lead electrocardiogram was taken each minute with paediatric size electrodes to maximise the chest area available for echocardiography. Heart rate and blood pressure were recorded every one to two minutes by a Critikon Dinamap vital signs monitor. Cross sectional echocardiography (Toshiba SSH-160A or 65A 3·75 MHz transducer) with the parasternal long and short axis (papillary muscle level) views and the apical four and two chamber views was continuous for up to 30 minutes after administration of dipyridamole. All studies were performed by one of us (JJ) and images were recorded on 12 mm VHS videotape for subsequent analysis. The time between coronary angiography and the dipyridamole study was 17 (SD 10) days; no significant cardiac events occurred during this period.

EXERCISE ELECTROCARDIOGRAPHY

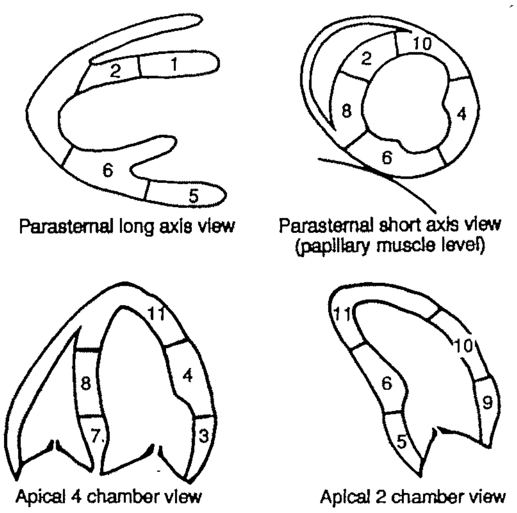
All patients had maximal modified Bruce treadmill exercise electrocardiography with a computerised ST segment analysis system (Case 12, Marquette)[5] and conventional end points. Both exercise stress and dipyridamole stress electrocardiograms were considered positive for ischaemia if there was ≥1 mm of new onset ST segment elevation or planar or downsloping ST segment depression 80 ms after the J point on three consecutive beats. The electrocardiograms were interpreted by an observer unaware of the other investigative findings. The interval between coronary angiography and exercise testing was 21 (10) days during which no important cardiac events occurred.

CARDIAC CATHETERISATION

Coronary arteriography was carried out with a Philips Poly Diagnost C imaging system and used the Judkins' technique and multiple views. Coronary stenoses, evaluated qualitatively by a single experienced observer unaware of the other results, were considered significant when the diameter of a major epicardial vessel was reduced by ≥70%.

IMAGE ANALYSIS

Cross sectional echocardiographic image analysis was performed blind from videotape playback by two independent experienced observers. Any disagreements were resolved by discussion. Wall motion was analysed by means of an 11 segment model of the left ventricle developed at the Hammersmith Hospital (figure); echocardiograms were read at baseline and peak stress and each segment was graded as normal or hyperkinetic, hypokinetic, akinetic, or dyskinetic. The development of a new abnormality of wall motion or worsening regional asynergy, defined as hypokinesis in any segment at baseline deteriorating to akinesis or dyskinesis with dipyridamole stress, was regarded as an abnormal response.



Parasternal long axis view

Parasternal short axis view (papillary muscle level)

Apical 4 chamber view

Apical 2 chamber view

1 Basal, anteroseptal
2 Mid, anteroseptal
3 Basal, lateral
4 Mid, lateral
5 Basal, inferior

6 Mid, inferior
7 Basal, posteroseptal
8 Mid, posteroseptal
9 Basal, anterior
10 Mid, anterior
11 Apical

Diagram of the Hammersmith Hospital 11 segment left ventricular model used for wall motion analysis.

STATISTICAL ANALYSIS

Continuous data are expressed as mean (SD). Paired or two sample t tests were performed as necessary and group comparisons were by one way analysis of variance. The χ^2 test with Yates' correction and McNemar's test were also used where appropriate. p Values $<0{\cdot}05$ were regarded as significant.

Results

HAEMODYNAMIC RESPONSE TO DIPYRIDAMOLE

The mean weight of the study population was 74 (12) kg and the mean dose of dipyridamole given was 63 (19) (range 20–101) mg. Table 2 shows the changes in haemodynamic variables by dipyridamole in patients with normal coronary arteries and in those with coronary disease; there were no significant differences in the haemodynamic response between these two groups. Similarly, no differences were found when patients with coronary disease and a wall motion abnormality at baseline ($n = 18$) were compared with those without ($n = 22$), and when patients with new or worsening transient asynergy ($n = 16$) were compared with those who showed a normal response ($n = 24$).

WALL MOTION ANALYSIS

Image quality during dipyridamole stress was adequate in the 55 subjects with satisfactory baseline studies. Transient hyperkinesis was the normal response to dipyridamole and this was particularly pronounced in the normally contracting segments of patients with a wall motion abnormality. Eighteen patients had asynergy at baseline. This involved one segment in eight, two segments in six, and three or more segments in four (table 1). New regional asynergy was seen in 11 patients and this was graded as akinesis in nine and hypokinesis in two; one patient with extensive akinesis in the area of the left anterior descending coronary artery and pronounced ST segment depression (9 mm in V5) also developed a transient dilated left ventricular cavity (table 1). Five of the 11 had two vessel disease, five had triple vessel disease, and one patient had normal coronary arteries and left ventricular hypertrophy secondary to essential hypertension. Transient dyskinesis of a segment hypokinetic at baseline developed in seven patients, and this was associated with remote new regional asynergy in one patient (table 1). All patients with coronary artery disease and a positive echocardiogram ($n = 16$) had a significant lesion in the vessel that supplied the abnormal segment. The sensitivity of dipyridamole stress echocardiography in one, two, and three vessel disease was 0%, 50%, and 58% respectively compared with 0%, 44%, and 58% for dipyridamole stress electrocardiography and 50%, 89%, and 92% for exercise electrocardiography. When asynergy at baseline was added to reversible asynergy to define an abnormal study, overall sensitivity improved from 40% to 60% whereas specificity remained unchanged at 93%

Table 2 Haemodynamic response to intravenous dipyridamole in patients with normal coronary arteries and with coronary artery disease

	Baseline Mean (SD)	*Peak stress Mean (SD)*	*Mean change*	*95% CI of mean change*	*p Value*
Normal coronary arteries (n = 15):					
HR (beats/min)	70 (14)	89 (25)	19	+8 to 29	0·002
Systolic BP (mm Hg)	138 (17)	134 (22)	−4	−18 to 9	NS
Diastolic BP (mm Hg)	84 (8)	78 (10)	−6	−12 to 1	NS
RPP (mm Hg/min)	9776 (2522)	12 207 (4417)	2431	367 to 4496	0·02
Coronary artery disease (n = 40):					
HR (beats/min)	72 (12)	91 (13)	19	+15 to 21	< 0·001
Systolic BP (mm Hg)	141 (21)	138 (16)	−3	−10 to 3	NS
Diastolic BP (mm Hg)	89 (15)	86 (10)	−3	−7 to 1	NS
RPP (mm Hg/min)	10 169 (2493)	12 532 (2730)	2363	1351 to 2838	<0·001

BP, blood pressure; 95% CI, 95% confidence interval; HR, heart rate; RPP, rate-pressure product.

(likelihood ratio = 9) (table 3). Visible collateral vessels at coronary angiography were present in 10 out of 16 patients (63%) with inducible asynergy, and in 13 out of 24 (54%) of the others. This difference was not significant. The observers agreed on wall motion analysis for 50 of 55 patients (91%).

DIPYRIDAMOLE STRESS ELECTROCARDIOGRAPHY

Significant ST segment depression had a sensitivity and specificity for coronary artery disease of 38% and 80% respectively (tables 1 and 3). Fifteen (50%) of 30 patients with multivessel disease had a positive dipyridamole stress electrocardiogram. Of the 10 patients with coronary disease who showed new asynergy on echocardiography, eight had a positive electrocardiogram. The site of ST segment change, usually leads V5 or V6, was not strictly related to the site of the wall motion abnormality. Only three of seven patients with worsening regional asynergy had significant ST segment depression. The one patient with a falsely positive dypridamole echocardiogram also had positive electrocardiographic changes with both dipyridamole stress and exercise.

EXERCISE TESTING

The peak heart rate and rate-pressure product on exercise for the entire group was 138 (28) beats/min and 23 121 (6802) mm Hg/min respectively. Table 3 shows the sensitivity and specificity of exercise electrocardiography. Nine of 10 coronary patients with new asynergy and six of seven with worsening asynergy had a positive exercise electrocardiogram (table 1). For patients with coronary artery disease, exercise duration in those with an abnormal echocardiographic response (n = 16) was 361 (146) seconds compared with 532 (177) seconds in the others (n = 24) (p < 0·01). Similarly, time to 1 mm ST segent depression was 201 (192) seconds in patients with reversible asynergy (n = 14) compared with 479 (158) seconds in those with a negative response (n = 18) (p < 0·01). Fourteen patients with coronary disease had significant ST segment deviation with both exercise and dipyridamole stress; the mean maximum extent of ST segment depression tended to be greater with exercise (2·3 (1·0) mm) than dipyridamole stress (2·0 (2·1) mm) but the difference was not significant.

SIDE EFFECTS

Table 4 documents the side effects experienced and treatment required after administration of dipyridamole. Chest pain developed in 13 of 16 (81%) patients with coronary disease and dipyridamole induced asynergy compared with nine (38%) of the other 24 (p = 0·02). One patient had prolonged ischaemia with severe chest pain for 30 minutes despite intravenous aminophylline (325 mg), but no evidence of myocardial infarction. Hypotension, defined as a fall in systolic blood pressure of ⩾30 mm Hg was seen in three cases. This was associated with sinus bradycardia in one patient and transient idioventricular rhythm in another. The third patient had an asystolic cardiac arrest preceded by chest pain and was promptly and succesfully resuscitated by treatment with aminophylline (200 mg) and atropine (1·2 mg).

Discussion

Some patients with suspected or definite coronary artery disease are unable to exercise because of peripheral vascular, orthopaedic, or neurological disease and others are poorly

Table 3 Comparative sensitivity, specificity, predictive value, and accuracy of dipyridamole stress echocardiography and dipyridamole stress and exercise electrocardiography

	Sensitivity (%)	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*Accuracy (%)*
Dipyridamole echo:					
New transient asynergy	10/40 (25)	14/15 (93)	10/11 (91)	14/44 (32)	24/55 (44)
New or worsening asynergy	16/40 (40)*	14/15 (93)†	16/17 (94)	14/38 (37)	30/55 (55)
Baseline or new asynergy	24/40 (60)	14/15 (93)	24/25 (96)	14/30 (47)	38/55 (69)
Dipyridamole ECG	15/40 (38)	12/15 (80)	15/18 (83)	12/37 (32)	27/55 (49)
Exercise ECG	32/40 (80)	10/15 (67)	32/37 (86)	10/18 (56)	42/55 (76)

ECG, electrocardiography; echo, cross sectional echocardiography.
*p < 0·01 *v* exercise ECG; †NS *v* exercise ECG.

motivated to achieve a sufficient workload.[6] Pharmacological stress induced by dipyridamole, combined with thallium scintigraphy or cross sectional echocardiography are alternative tests in such cases.[6] Because echocardiography involves no exposure to radiation, is quicker and cheaper and, in general, more readily accessible than perfusion imaging we studied the utility and safety of this approach.

Dipyridamole blocks adenosine uptake into erythrocytes and endothelium, potentiating its dilatatory action on small vessels.[4] This leads to a fall in perfusion pressure distal to coronary stenoses and flow redistribution from endocardium to epicardium causing perfusion defects to become visible on thallium scintigraphy or, if more severe, myocardial ischaemia and regional asynergy on echocardiography.[4] The increase in rate-pressure product and fall in diastolic blood pressure (table 2) are probably less important. Haemodynamic variables changed similarly in all groups; perhaps a reflection of exaggerated hyperkinesis of the normally perfused myocardium in those patients with coronary disease.

Margonato *et al* at this centre used 0·6 mg/kg of dipyridamole to study 21 patients with multivessel disease and a positive exercise electrocardiogram. They found that only patients with severely limited coronary flow reserve and exercise capacity were likely to have a positive echocardiogram. The vessel where flow reserve was most impaired could be identified, however, despite the non-physiological nature of the stress.

Picano *et al* found improved test sensitivity with high dose infusion of dipyridamole[7,8] and we used this combined with multiple imaging views rather than a single projection as reported by Margonato *et al.*[3] Fifteen patients with normal coronary arteries were also studied to obtain information on test specificity. Sixteen (53%) of 30 patients with multivessel disease had new or worsening asynergy compared with 11 (52%) of 21 patients studied by Margonato *et al.*[3] Exercise duration and time to 1 mm ST segment depression were significantly shorter in those with a positive echocardiogram, all of whom had a tight stenosis in the vessel that supplied the abnormal segment. The coronary reserve and angiographic severity of multivessel disease in these two studies were similar. We therefore cannot confirm that the use of high dose dipyridamole improves sensitivity.

Table 4 Side effects and treatment required after high dose dipyridamole stress in 55 patients

	CAD (n = 40)	*Normal (n = 15)*	*Total (%)*
Side effect:			
Chest pain	22	5	27 (49)
Headache	7	10	17 (31)
Dizziness	5	4	9 (16)
Dyspnoea	5	0	5 (9)
Nausea	3	2	5 (9)
Arrhythmia	3	1	4 (7)
Hypotension with syncope	1	1	2 (4)
Cardiac arrest	1	0	1 (2)
Vomiting	1	0	1 (2)
Total	26	11	37 (67)
Treatment:			
Aminophylline	9	1	10 (18)
Nitrates	3	0	3 (5)
Atropine	2	1	3 (5)
Total	11	1	12 (22)

CAD, coronary artery disease.

None of the 10 patients with single vessel disease had an abnormal stress echocardiogram. This limitation has also been noted by Kern *et al* who were able to provoke new regional asynergy with intravenous dipyridamole in only three (23%) of 13 patients with critical single vessel disease.[9] Similarly Fung *et al*, who used dipyridamole stress to study open chest dogs with a severe coronary stenosis, found echocardiographically detectable dysfunction in only 55% of animals.[10] Dipyridamole stress echocardiography seems less sensitive than dipyridamole stress thallium scintigraphy.[3,11] A possible explanation is that small thallium defects, more likely in single vessel disease, may not be associated with an abnormality of wall motion. Also, apparent perfusion defects may only be relative because dipyridamole increases flow in the myocardium supplied by healthy vessels. Stress induced by intravenous adenosine infusion, which is limited by troublesome side effects at higher infusion rates, also seems more sensitive than echocardiography in the detection of coronary artery disease with perfusion imaging.[12,13]

Seven patients had worsening regional asynergy; in each case hypokinesis deteriorated to dyskinesis. Although a baseline wall motion abnormality was present in all seven, this was subtle in three instances and could easily have been overlooked. Whereas worsening asynergy is compatible with ischaemia of the remaining viable myocardium in an infarct zone, the change in regional loading induced by dipyridamole is a possible alternative explanation. Both mechanisms may contribute to different degrees in individual patients.

Dipyridamole administration in standard doses of 0·56 mg/kg seems to be relatively safe.[14,15] Serious complications, including death,[16] myocardial infarction,[14] prolonged myocardial ischaemia,[17] and cardiac arrest,[18,19] have been reported, though rarely. Information on the safety of higher doses is incomplete but, in our experience, side effects and severe reactions are more common. One of our patients who had three vessel disease developed prolonged myocardial ischaemia and another had an asystolic cardiac arrest that was preceded by chest pain and new regional asynergy which suggested an ischaemic basis. Two patients developed hypotension, bradycardia, and syncope. This may reflect adenosine induced depression of cardiac conduction tissue with peripheral vasodilation because one had normal coronary arteries and neither had evidence of preceding ischaemia. Both responded promptly to aminophylline and atropine. High dose dipyridamole may be more hazardous in elderly patients, who tolerate hypotension poorly and more frequently have occult disease of the conduction tissue. Only five of our patients were 70 or older.

The use of high dose dipyridamole stress during cross sectional echocardiography did not seem to improve diagnostic accuracy in coronary artery disease and resulted in more frequent, and occasionally severe, side effects. Further work is needed to determine whether digital echocardiographic techniques, which allow side by side comparison of wall segments before and after drug intervention, improve sensitivity.[20]

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1 Sawada SG, Ryan T, Fineberg NS, *et al.* Exercise echocardiographic detection of coronary artery disease in women. *J Am Coll Cardiol* 1989;14:1440–7.

2 Iskandrian AS, Heo J, Askenase A, Segal BL, Auerbach N. Dipyridamole cardiac imaging. *Am Heart J* 1988; 115:432–43.

3 Margonato A, Chierchia S, Cianflone D, *et al.* Limitations of dipyridamole-echocardiography in effort angina pectoris. *Am J Cardiol* 1987;59:225–30.

4 Picano E. Dipyridamole-echocardiography test: historical background and physiologic basis. *Eur Heart J* 1989; 10:365–76.

5 Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85: 546–62.

6 Stratmann HG, Kennedy HL. Evaluation of coronary artery disease in the patient unable to exercise: alternatives to exercise stress testing. *Am Heart J* 1989;117:1344–65.

7 Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Comparison of the high-dose dipyridamole-echocardiography test and exercise two-dimensional echocardiography for diagnosis of coronary artery disease. *Am J Cardiol* 1987;59:539–42.

8 Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. High-dose dipyridamole echocardiography test in effort angina pectoris. *J Am Coll Cardiol* 1986;8:846–54.

9 Kern MJ, Pearson AC, Labovitz AJ, *et al.* Effects of pharmacologic coronary hyperemia on echocardiographic left ventricular function in patients with single vessel coronary artery disease. *J Am Coll Cardiol* 1989;13: 1042–51.

10 Fung AY, Gallagher KP, Buda AJ. The physiologic basis of dobutamine as compared with dipyridamole stress interventions in the assessment of critical coronary stenosis. *Circulation* 1987;76:943–51.

11 Younis LT, Chaitman BR. Update on intravenous dipyridamole cardiac imaging in the assessment of ischaemic heart disease. *Clin Cardiol* 1990;13:3–10.

12 Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–7.

13 Nguyen T, Heo J, Ogilby D, Hare T, Weber J, Iskandrian A. Adenosine-SPECT thallium-201 myocardial imaging [abstract]. *J Am Coll Cardiol* 1990;15:229A.

14 Ranhosky A, Kempthorne-Rawson J, and the Intravenous Dipyridamole Thallium Imaging Study Group. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990;81:205–9.

15 Homma S, Gilliland Y, Guiney TE, Strauss HW, Boucher CA. Safety of intravenous dipyridamole for stress testing with thallium imaging. *Am J Cardiol* 1987;59:152–4.

16 Friedman HZ, Goldberg SF, Hauser AM, O'Neill WW. Death with dipyridamole-thallium imaging [letter]. *Ann Intern Med* 1988;109:990–1.

17 Lewen MK, Labovitz AJ, Kern MJ, Chaitman BR. Prolonged myocardial ischaemia after intravenous dipyridamole thallium imaging. *Chest* 1987;92:1102–4.

18 Bayliss J, Pearson M, Sutton GC. Ventricular dysrhythmias following intravenous dipyridamole during "stress" myocardial imaging. *Br J Radiol* 1983;56:686.

19 Blumenthal MS, McCauley CS. Cardiac arrest during dipyridamole imaging. *Chest* 1988;93:1103–4.

20 Cohen JL, Greene TO, Alston JR, Wilchfort SD, Kim CS. Usefulness of oral dipyridamole digital echocardiography for detecting coronary artery disease. *Am J Cardiol* 1989;64:385–6.

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Are enzymatic tests good indicators of coronary reperfusion?

Hans A Bosker, Arnoud van der Laarse, Volkert Manger Cats, Albert V G Bruschke

Abstract

***Objective*—To assess the accuracy of four enzymatic tests, including early release rates of creatine kinase and α-hydroxybutyrate dehydrogenase, in assessing coronary reperfusion after thrombolytic therapy.**

***Design*—A prospective clinical trial identifying patients with a successful thrombolytic treatment.**

***Patients*—Eighty nine patients with acute myocardial infarction were studied. Arteriography showed a closed infarct related artery in all of them. Reperfusion due to thrombolysis occurred in 74 patients and there was no reperfusion in 15 patients.**

***Results*—The 74 patients showing coronary reperfusion had a significantly shorter time to peak creatine kinase activity, higher early release rates for creatine kinase and α-hydroxybutyrate dehydrogenase, and a more rapid release of α-hydroxybutyrate dehydrogenase (ratio of cumulative release of α-hydroxybutyrate dehydrogenase during the first 24 hours to that 72 hours after infarction). All these differences were statistically significant ($p < 0{\cdot}001$). Optimum cut off levels were determined with decision level plots and the accuracy of the four enzymatic tests was calculated. Accuracy was low for all four tests (73%, 70%, 70%, and 82%).**

***Conclusion*—None of the four enzymatic tests accurately predicted the perfusion state of the infarct related coronary artery after thrombolysis. These tests cannot be used reliably in routine clinical practice as non-angiographic markers of coronary reperfusion.**

Thrombolytic therapy for acute myocardial infarction is used to achieve reperfusion of the infarct related coronary artery. Intracoronary thrombolysis needs emergency cardiac catheterisation and so is of limited value. This has led to widespread use of intravenous administration of thrombolytic drugs. Hence, reliable methods, other than angiographic evidence, are needed to detect coronary reperfusion. In previous studies, relief of chest pain,[1-3] resolution of ST segment elevations,[4 5] and occurrence of specific arrhythmias[6-8] were used as markers of reperfusion. Also, after reperfusion of an acutely occluded coronary artery early peaking of plasma creatine kinase ar creatine kinase MB activity[9-12] as well as oth cardiac enzymes[13 14] were found. These no invasive criteria are neither sensitive n specific, however, as indicators of recanalis tion.[15 16] Even when they are used in combin tion, their predictive accuracy is high on when they are concordant. Unfortunatel concordance occurs in only 14% of patien with reperfusion and in 79% of patients wit out.[15] Recently, several investigators ha evaluated the rapid initial increases in plasm creatine kinase and creatine kinase M activity as non-angiographic markers of repe fusion.[17-19] The onset of these increases close reflected the time of angiographic document tion of reperfusion. As indicators of coronar artery reperfusion they seemed to be high sensitive and specific.

Analogous to this rapid initial increase i plasma creatine kinase activity anoth enzymatic marker of reperfusion could be th rapid initial increase in plasma activity of c hydroxybutyrate dehydrogenase. To dete mine the accuracy of enzymatic tests in asses ing coronary reperfusion we compared fo different enzymatic variables: (1) the time t peak creatine kinase activity; (2) the earl release rate of creatine kinase activity; (3) th early release rate of α-hydroxybutyrat dehydrogenase; and (4) the rate of α hydroxybutyrate dehydrogenase releas represented by the ratio of quantities release in 24 hours and 72 hours. The diagnosti effectiveness and efficiency of these tests wer evaluated by cumulative distribution analysi graphs[20] (as an alternative to receiver operat ing characteristic curves[21]) and decision lev curves.[22]

Methods

PATIENTS

Patients studied were part of a prospectiv trial with 201 consecutive patients treate with intravenous and intracoronary strepto kinase for acute myocardial infarction accord ing to a standardised protocol (750 000 I intravenous streptokinase and 250 000 I intracoronary streptokinase). The aims of thi prospective trial were to identify patients wit a successful thrombolytic treatment and t study the effects of elective percutaneou transluminal coronary angioplasty (PTCA which was used for prophylactic reasons afte successful thrombolysis. Acute coronar angiography was performed in all patient Only patients with an occluded infarct relate

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artery before the start of intracoronary streptokinase infusion were included in the present analysis. Two groups of patients were compared: (1) patients without reperfusion—namely, those in whom the infarct related artery remained occluded at the end of intracoronary administration of streptokinase (Thrombolysis in Myocardial Infarction Trial (TIMI) grade 0 or 1[23]), and (2) patients with reperfusion—that is, with a patent infarct related artery at the end of intracoronary infusion of streptokinase (TIMI grade 2 or 3). Patients without a significant rise in serum enzymes, defined as a cumulative release of α-hydroxybutyrate dehydrogenase in the first 72 hours ⩽150 U/l, were excluded from the analysis, as they had minimal or no myocardial necrosis after successful thrombolytic therapy. Other exclusion criteria were first blood sample taken ⩾ six hours after the onset of symptoms and an interval of ⩾10 hours between the first two blood samples.

MEASUREMENTS OF SERUM ENZYME ACTIVITIES

Samples of 5 ml of venous blood were obtained at admission, then every six hours until creatine kinase activity reached its highest value and thereafter daily for the next three days. The blood samples were allowed to clot and the activities (U/l) of creatine kinase and α-hydroxybutyrate dehydrogenase in the serum were measured with an autoanalyser (DuPont ACA) in the Department of Clinical Chemistry at our hospital.

CALCULATION OF CUMULATIVE α-HYDROXYBUTYRATE DEHYDROGENASE

Van der Laarse *et al* used a two compartment model to account for the kinetics of myocardial proteins between the intravascular and extravascular spaces.[24] We used this model to calculate the amount of α-hydroxybutyrate dehydrogenase that entered a litre of plasma up to a certain time. The total α-hydroxybutyrate dehydrogenase activity released by the infarcted myocardium in the first 24 hours (Q_{24}) and the first 72 hours (Q_{72}) were calculated and expressed in U/l; Q_{72} is considered to represent the ultimate infarct size.[24]

CALCULATION OF EARLY RELEASE RATE OF CREATINE KINASE AND α-HYDROXYBUTYRATE DEHYDROGENASE

For both enzymes the difference in total activity of the first two samples was divided by the time between these samples. This gave the early release rate of enzyme expressed in U/l/h.

CALCULATION OF α-HYDROXYBUTYRATE DEHYDROGENASE RELEASE RATE

Another method to measure the rate at which α-hydroxybutyrate dehydrogenase which is released from the myocardium into the circulation is to calculate the ratio of the quantities of α-hydroxybutyrate dehydrogenase released in the first 24 hours and the first 72 hours (Q_{24}/Q_{72}). This method was also used in the randomised streptokinase trial conducted by The Netherlands Interuniversity Cardiology Institute.[13]

ANALYSIS

For comparative analysis we used cumulative distribution analysis graphs,[20] directly plotting sensitivity and specificity against all possible cut off points. To select the optimum decision threshold a decision level curve was used,[22] with which the difference between the true positive rate (sensitivity) and the false positive rate (100-specificity) was plotted against all possible cut off levels.

The Mann-Whitney rank sum test was used to assess differences between means of data in reperfused and non-reperfused patients. Two tailed p values are reported. A p value of $<0{\cdot}05$ was regarded as statistically significant.

Results

From September 1987 to July 1989, 201 consecutive patients were treated with intravenous and intracoronary streptokinase for acute myocardial infarction according to a standardised protocol. The initial coronary angiogram showed that the infarct related coronary artery was patent in 89 patients (44·3%). These patients were excluded from the analysis. Twenty three of the 112 remaining patients were excluded because of (*a*) minimal or no myocardial necrosis—that is, a Q_{72} ⩽150 U/l (one patient), (*b*) time of first blood sample ⩾six hours after onset of infarction (four patients), (*c*) time interval between the first two blood samples ⩾10 hours (seven patients), and (*d*) incomplete data due to early death in hospital or transfer to other departments (11 patients).

Thus 89 patients formed our study population; 74 showed reperfusion of the infarct related artery after intracoronary streptokinase and 15 showed no reperfusion.

Table 1 presents the results of the four enzymatic tests for these patients. Reperfused patients showed a shorter time to peak creatine kinase activity, more rapid early release rates of creatine kinase and α-hydroxybutyrate dehydrogenase and also a higher Q_{24}/Q_{72} ratio than non-reperfused patients. The differences between groups were highly significant for all enzymatic tests. The enzymatic infarct size as measured by cumulative release of α-hydroxybutyrate dehydrogenase during the first 72 hours (Q_{72}) was not different between groups.

Figure 1 presents the cumulative distribution analysis graphs for the four enzymatic tests. It seemed that none of the four tests was sufficiently sensitive or specific to assess reperfusion. Using decision level plots, we determined the optimum decision threshold value for all four enzymatic tests and measured sensitivity, specificity, accuracy, and the predictive values of a positive test and a negative test. Accuracy is defined as true positives plus true negatives divided by the number of patients tested. Table 2 summarises the results. Despite optimal cut off values the accuracy of the tests was low with 82% as the highest value for Q_{24}/Q_{72}. The predictive value of a negative test was very low for all tests. The ratio Q_{24}/Q_{72} had the best predictive value of a negative test (50%). This is still low and not

Table 1 Results of enzymatic tests for reperfusion in patients with reperfused and non-reperfused infarct related coronary arteries as documented angiographically

Variable	*Reperfusion (mean (SD))*	*No reperfusion (mean (SD))*	*p Value**
No of patients	74	15	
Time to peak CK (h)	13·1 (8·3)	24·0 (8·5)	<0·0001
Early release rate of CK (U/1/h)	89·3 (84·8)	29·2 (28·9)	0·0008
Early release rate of HBDH (U/1/h)	54·9 (49·3)	17·6 (17·4)	0·0005
Release rate of HBDH (Q_{24}/Q_{72})	0·65 (0·16)	0·50 (0·09)	0·0002
Enzymatic infarct size (Q_{72} (U/1))	1336 (841)	1213 (587)	NS

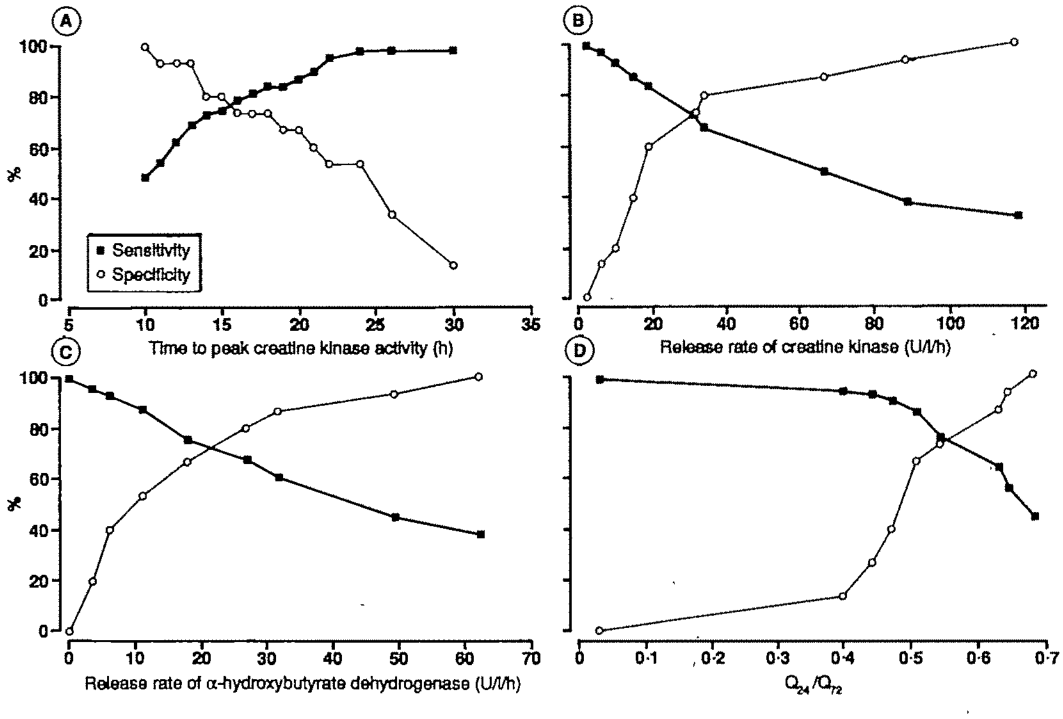
*Mann-Whitney rank sum test (two sided).
CK creatine kinase; HBDH, α-hydroxybutyrate dehydrogenase.

relevant for clinical practice. The predictive value of a positive test was high for all tests but this was due to a high pretest probability for a positive test result.

Discussion

The results, using the methods in this study, show that none of the four enzymatic tests is accurate enough to be of clinical use in identifying coronary reperfusion. These observations contrast with the findings of Garabedian *et al*, Lewis *et al*, and Ong *et al*.[17–19] Neither the early increase in creatine kinase activity nor the early increase of α-hydroxybutyrate dehydrogenase was accurate (70% for both; table 2) in assessing the reperfusion state of the infarct related artery. In comparison with the other investigations there are differences in methods and the definition of reperfusion. In the other studies[17–19] blood samples for enzyme measurements were taken at shorter intervals (15–120 minutes) than ours. Ong *et al* stated, for their reperfusion model, that the most important discriminating factor between reperfusion and non-reperfusion is the time to onset of increase in creatine kinase MB activity.[19] In the case of reperfusion, the initial increase occurred at the time of reperfusion; there was an early rapid rate of increase, which then progressively declined. So, with a longer interval between taking the first two blood samples, as in our study, the initial rapid increase rate could be missed. Garabedian *et al* and Lewis *et al* also determined the rate of increase in creatine kinase MB activity in the very early phase of reperfusion and found that several empirical estimates of the rate of increase could differentiate between patients with reperfusion and without.[17 18]

The definition of reperfusion is not the same for all studies mentioned earlier. Garabedian *et al* defined reperfusion as complete distal opacification of the previously occluded coronary artery (TIMI grade 2 or 3).[17] The same definition was used in our study. This definition includes patients with slow and rapid filling of the distal part of the coronary artery, and hence with slow and rapid appearance patterns of cardiac enzymes. Lewis and coworkers, however, studied only reperfused patients with a complete and rapid filling of the infarct related artery (TIMI grade 3), and they found that the rates of absolute increase in creatine kinase and creatine kinase MB activity completely separated the patients with from the patients without reperfusion.[18] These findings indicate that a rapid initial increase in cardiac enzyme activity in plasma depends upon the re-establishment of perfusion with normal coronary blood flow rather than simply patency of the infarct related artery. Although in our study reperfused patients showed a shorter time to peak creatine kinase activity and more rapid early release rates of creatine kinase and α-hydroxybutyrate dehydrogenase than non-reperfused patients, and the differences reached significance, we could not determine an index of coronary artery reperfusion with plasma enzyme tests that clearly distinguished between reperfused and non-reperfused patients. Even the optimum cut off points for the different



Cumulative distribution analysis graphs for the four enzyme tests.

Table 2 Sensitivity, specificity, accuracy, and predictive values at optimal decision threshold levels of four enzymatic tests for reperfusion applied to patients with acute myocardial infarction having reperfusion (74) and no reperfusion (15), after early thrombolytic therapy.

Enzymatic test	*Decision threshold*	*Sensitivity*	*Specificity*	*Accuracy*	*PV+*	*PV−*
Time to peak CK (h)	≤13	69	93	73	98	38
Early release rate CK (U/1/h)	≥34·1	68	80	70	94	33
Early release rate HBDH (U/1/h)	≥27·0	68	80	70	94	33
Release rate HBDH (Q_{24}/Q_{72})	≥0·51	86	67	82	93	50

All values are in percentages.
PV+, predictive value of a positive test result; PV−, predictive value of a negative test result; CK, creatine kinase; HBDH, α-hydroxybutyrate dehydrogenase.

tests determined with the use of decision level curves were not useful to separate reperfused from non-reperfused patients. These findings indicate that the rapid release of cardiac enzymes after reperfusion does not depend on reperfusion alone but also depends on several other factors. The recovery of coronary blood flow after recanalisation affects the rate of appearance of cardiac enzymes, which is in accordance with the bi-exponential model of Ong *et al.*[19] Another factor is the ultimate size of infarction. When the amount of necrosis is small and the total release of enzyme activity (Q_{72}) is low, the early release rate will also be low and may approach the values seen in patients without reperfusion. Also, the interval between infarction and reperfusion determines the early release rate of cardiac enzymes. In late reperfusion, irreversible microvascular changes occur and nutritive flow is not completely re-established even with a patent infarct related coronary artery.[25 26] Therefore, even with successful thrombolysis in late reperfusion, the pattern of appearance of cardiac enzymes may resemble that of permanent occlusion. These factors can easily explain the overlap in early release rate of creatine kinase or α-hydroxybutyrate dehydrogenase from reperfused and non-reperfused patients, making these enzymatic tests of little use in routine clinical practice.

Early reocclusion of the infarct related artery after initial successful thrombolysis may also be responsible for the discrepancy between enzymatic indices of reperfusion taken over a long period (24 hours) and angiographic assessment of reperfusion obtained during the 30 minute period of intracoronary infusion of streptokinase. We found no symptomatic reocclusion during the first 24 hours after recanalisation, however. Early asymptomatic reocclusion cannot be excluded because early repeated coronary arteriography was not performed, but it is unlikely to have occurred in many cases.

With regard to intravenous thrombolysis it is of great importance to detect accurately and in an early phase patients with persistent occlusion of the infarct related artery despite thrombolytic treatment, because these patients might benefit from further interventional procedures such as "rescue" PTCA to restore coronary blood flow.[27 28] The predictive value of a negative test result is very low for all enzymatic tests (table 2), especially for the early release rates of creatine kinase and α-hydroxybutyrate dehydrogenase, the two tests that will give a result within the first hours of infarction, when rescue PTCA may be considered. In the presence of a low pretest probability of non-reperfusion, enzymatic tests will not discriminate accurately between patients with and without reperfusion of the infarct related coronary artery. It seems likely that other more refined or sophisticated assays, such as those for creatine kinase isoforms,[29 30] have the same limitations in predicting coronary reperfusion because their rate of appearance is affected by the same factors as affect the enzymes we measured.

Possibly the results would have been improved if we had taken blood samples more frequently; however, a high sampling rate makes the test cumbersome in routine clinical practice. It seems that currently only coronary arteriography allows accurate assessment of the perfusion state of the infarct related artery, particularly in the very early stage of myocardial infarction when further interventional procedures may still be beneficial to the patient.

1 Rentrop KP, Blanke H, Karsch KR, *et al.* Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 1981;63:307–15.
2 Lee G, Amsterdam EA, Low R, *et al.* Efficacy of percutaneous transluminal coronary recanalisation utilising streptokinase thrombolysis in patients with acute myocardial infarction. *Am Heart J* 1981;102:1159–67.
3 Ganz W, Geft I, Maddahi J, *et al.* Nonsurgical reperfusion in evolving myocardial infarction. *J Am Coll Cardiol* 1983; 1:1247–53.
4 Krucoff MW, Green CE, Satler LF, *et al.* Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. *Am J Cardiol* 1986;57:916–22.
5 Hackworthy RA, Vogel MB, Harris PJ. Relationship between changes in ST segment elevation and patency of the infarct-related coronary artery in acute myocardial infarction. *Am Heart J* 1986;112:279–84.
6 Cercek B, Lew AS, Laramee P, *et al.* Time course and characteristics of ventricular arrhythmias following reperfusion in acute myocardial infarction. *Am J Cardiol* 1987;60:214–8.
7 Goldberg S, Greenspon AJ, Urban PL, *et al.* Reperfusion arrhythmia: a marker of restoration of antegrade flow during intracoronary thrombolysis for acute myocardial infarction. *Am Heart J* 1983;105:26–32.
8 Gorgels AP, Letsch IS, Bär FW, Jansen JH, Wellens HJ. Accelerated idioventricular rhythm in persistent ischemic chest pain indicates necrosis and reperfusion [abstract]. *Circulation* 1986;74(suppl II):11.
9 Roberts R, Ishikawa Y. Enzymatic estimation of infarct size during reperfusion. *Circulation* 1983;68(suppl I):83–9.
10 Shell W, Mickle DK, Swan HJC. Effects of nonsurgical myocardial reperfusion on plasma creatine kinase kinetics in man. *Am Heart J* 1983;106:665–9.
11 Blanke H, Von Hardenberg D, Cohen M, *et al.* Patterns of creatine kinase release during acute myocardial infarction after nonsurgical reperfusion: coamparison with conventional treatment and correlaton with infarct size. *J Am Coll Cardiol* 1984;3:675–80.
12 Gore JM, Roberts R, Ball SP, *et al.* Peak creatine kinase as a measure of effectiveness of thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1987;59:1234–8.
13 Van der Laarse A, Vermeer F, Hermens WT, *et al.* Effects of early intracoronary streptokinase on infarct size estimated from cumulative enzyme release and on enzyme release

rate: a randomised trial of 533 patients with acute myocardial infarction. *Am Heart J* 1986;112:672–81.
14 Van der Laarse A, Van der Wall EE, Van den Pol RC, *et al.* Rapid enzyme release from acutely infarcted myocardium after early thrombolytic therapy: washout or reperfusion damage? *Am Heart J* 1988;115:711–6.
15 Kircher BJ, Topol EJ, O'Neill WW, *et al.* Prediction of infarct coronary artery recanalization after intravenous thrombolytic therapy. *Am J Cardiol* 1987;59:513–5.
16 Califf RM, O'Neill WW, George BS, *et al.* Failure of simple clinical measurements to predict reperfusion status after intravenous thrombolysis. *Ann Intern Med* 1988;108: 658–62.
17 Garabedian HD, Gold HK, Yasuda T, *et al.* Detection of coronary artery reperfusion with creatine kinase-MB determinations during thrombolytic therapy: correlation with acute angiography. *J Am Coll Cardiol* 1988;11: 729–34.
18 Lewis BS, Ganz W, Laramee P, *et al.* Usefulness of a rapid initial increase in plasma creatine kinase activity as a marker of reperfusion during thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1988;62:20–4.
19 Ong L, Coromilas J, Zimmerman JM, *et al.* A physiologically based model of creatine kinase-MB release in reperfusion of acute myocardial infarction. *Am J Cardiol* 1989;64:11–5.
20 Krouwer JS. Cumulative distribution analysis graphs—an alternative to ROC curves. *Clin Chem* 1987;33:2305.
21 Beck JR, Schultz EK. The use of relative operating characteristic (ROC) curves in test performance evaluation. *Arch Pathol Lab Med* 1986;110:13–20.
22 Ward CD. The differential positive rate, a derivative of receiver operating characteristic curves useful in comparing tests and determining decision levels. *Clin Chem* 1986;32:1428–9.
23 The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I findings. *N Engl J Med* 1985;312:932–6.
24 Van der Laarse A, Hermens WT, Hollaar L, *et al.* Assessment of myocardial damage in patients with acute myocardial infarction by serial measurement of serum alpha-hydroxybutyrate dehydrogenase levels. *Am Heart J* 1984; 107:248–60.
25 Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786–94.
26 Sobel BE, Bergmann SR. Coronary thrombolysis: some unresolved issues. *Am J Med* 1982;72:1–4.
27 Fung AY, Lai P, Topol EJ, *et al.* Value of percutaneous transluminal coronary angioplasty after unsucessful intravenous streptokinase therapy in acute myocardial infarction. *Am J Cardiol* 1986;58:686–91.
28 Califf RM, Topol EJ, George BS, *et al.* Characteristics and outcome of patients in whom reperfusion with intravenous tissue-type plasminogen activator fails: results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I trial. *Circulation* 1988;77:1090–9.
29 Nohara R, Myears DW, Sobel BE, Abendschein DR. Optimal criteria for rapid detection of myocardial reperfusion by creatine kinase MM isoforms in the presence of residual high grade coronary stenosis. *J Am Coll Cardiol* 1989;14:1067–73.
30 Abendschein DR. Rapid diagnosis of myocardial infarction and reperfusion by assay of plasma isoforms of creatine kinase isoenzymes. *Clin Biochem* 1990;23:399–407.

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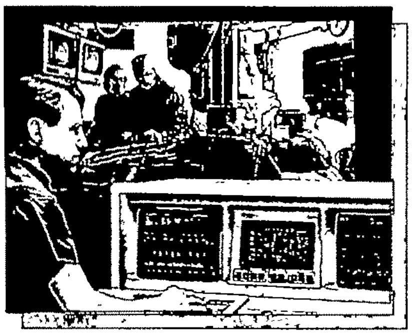

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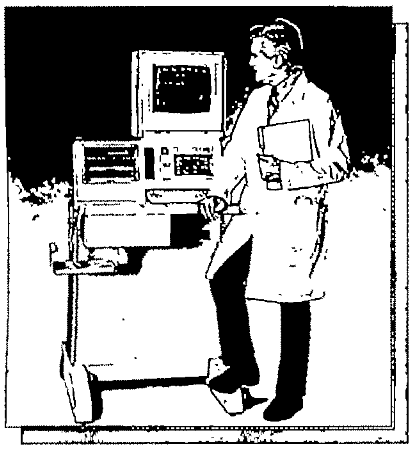

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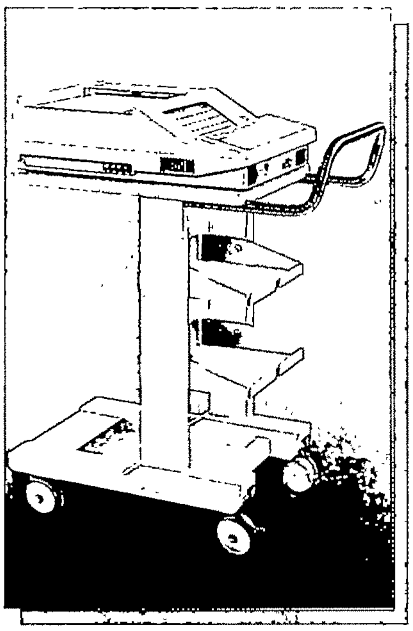

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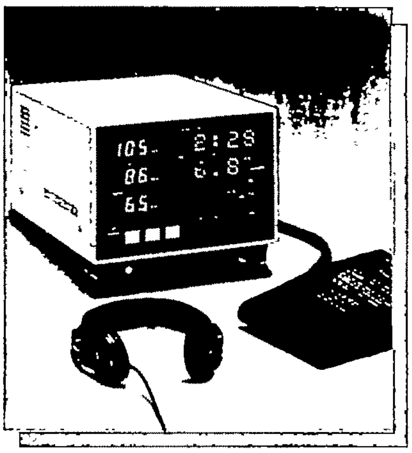

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989
63, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**
293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

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Long term course and cardiac sympathetic nerve activity in patients with hypertrophic cardiomyopathy

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Abstract

***Objective*—To investigate the relation between regional myocardial sympathetic nerve activity and the electrocardiographic and cardiac functional changes in hypertrophic cardiomyopathy.**

***Design*—A retrospective study to compare the findings of myocardial scintigraphy with iodine-123 metaiodobenzylguanidine (MIBG) and the serial electrocardiographic changes.**

***Setting*—Myocardial scintigraphy was performed with iodine-123 MIBG and thallium-201 and single photon emission computed tomography (SPECT) in the division of nuclear medicine of Kanazawa University Hospital. Both SPECT studies were performed within a week.**

***Patients*—22 patients with hypertrophic cardiomyopathy classified according to their serial electrocardiographic changes—namely, 15 patients with an increase in or the appearance of a negative T wave (group A) and seven patients with a conduction disturbance or a decrease in or disappearance of the negative T wave (group B). The mean follow up period was 45 (range 12–143) months.**

***Results*—Group B showed a high rate of decreased activity or defects in MIBG uptake compared with group A (p < 0·005). The areas of decreased activity or defects corresponded with the hypertrophied portion of the left ventricular wall. Although the early myocardial uptake (MIBG: thallium ratio) was similar in both groups, the mean (SD) MIBG clearance rate was significantly higher (p < 0·05) in group B (0·25 (0·17)) than in group A (0·10 (0·15)).**

***Conclusion*—Abnormalities of regional myocardial sympathetic nerve activity may be important in patients with hypertrophic cardiomyopathy and suspected progression of myocardial damage.**

The clinical course of hypertrophic cardiomyopathy varies considerably. Some patients remain symptom free for many years, whereas others die suddenly or develop congestive heart failure after a short time. Cases in which the disease progresses to a dilated cardiomyopathy, with left ventricular dilatation, left ventricular wall thinning, and left ventricular systolic impairment, have also been reported.[1–3] Electrocardiographic changes, particularly in T waves, occur in hypertrophic cardiomyopathy. We examined the relation between these T wave and functional changes, and reported that cardiac function was depressed in patients in whom a negative T wave decreased or disappeared.[4] It is not known how localised sympathetic nerve activity in the heart is involved in these changes.

Meta-iodobenzylguanidine (MIBG) is a guanetidine analogue known to produce effects similar to those of noradrenaline. For this reason scintigraphy with radiolabelled analogues shows promise as an aid in the study of the role of sympathetic nerve innervation in heart function.[5–7] In the present study we used MIBG to investigate the relation between sympathetic nerve activity in different myocardial regions and the electrocardiographic and cardiac functional changes that occur in hypertrophic cardiomyopathy.

Patients and methods

PATIENTS

We studied 22 patients with hypertrophic cardiomyopathy in whom electrocardiographic changes could be serially followed for more than 12 months. Hypertrophic cardiomyopathy was diagnosed in 20 of these patients by cardiac catheterisation with endomyocardial biopsy and in the remaining two patients by electrocardiographic and echocardiographic testing. As judged by left ventriculography, biventriculography, and echocardiography, hypertrophy, mainly of the interventricular septum, was present in 19 patients, hypertrophy of the apical portion in two patients, and global hypertrophy in one patient. The disease was non-obstructive in 20 and obstructive in two patients. The 22 patients were classified into two groups based on the serial electrocardiographic changes. Group A consisted of those who showed an unchanged T wave, positive T wave disappearance, or negative T wave deepening of more than 0·5 mV, during the study. Group B consisted of patients whose negative T wave decreased by more than 0·5 mV or those in whom the conduction system was disturbed. There were 15 patients (11 men and four women) in group A, and seven patients (four men and three women) in group B. In group A 12 patients were in New York Heart

York Heart Association class I and three were in class II. In group B four were in class II and three were in class III.

SCINTIGRAPHY

The patients were instructed to fast on the day of the radionuclide study and to continue the fast until the study ended. The patients received their usual medications, which included calcium channel blockers and antiarrhythmic agents. No patient was receiving reserpine or tricyclic antidepressants. All patients gave their informed consent to the protocol of MIBG imaging as part of a clinical trial.

An intravenous injection of 140–180 MBq (3·8–4·9 mCi) of ^{123}I-MIBG was given between 9.00 and 10.00 am and the first and second single photon emission computed tomography (SPECT) studies were started about 20 minutes and three hours thereafter. The SPECT system (Shimazu ZLC 7500-scintipac 700) consisted of a dual headed scintillation camera equipped with high resolution, low energy, parallel hole collimators. A total of 60 projection images were obtained over 360° in 6° increments with 30 seconds for each view. After preprocessing of the projection images with nine point weighted smoothing, transaxial tomographic slices were reconstructed by use of Shepp-Logan's filtered back projection algorithm. Neither a scatter correction nor an absorption correction was applied.

The thallium-201 SPECT study was performed within a week of the MIBG study with only a resting image obtained. Data acquisition was started 15 minutes after the administration of 120 MBq (3·2 mCi) thallium-201. The acquisition conditions and reconstruction method were the same as those of the MIBG study.

DATA ANALYSIS

The SPECT data were analysed as follows: rectangular regions of interest, usually 5 × 5 pixels in size, were placed over the septum, apex, lateral wall, lung, and mediastinum in both the ^{123}I-MIBG and ^{201}Tl transaxial images. To calculate the absolute uptake, an 8 ml vial containing 7·4 MBq (0·2 mCi) of either ^{123}I-MIBG or ^{201}Tl was placed in the centre of rotation in air and the SPECT count in the reconstructed image was measured. A cross calibration factor between the SPECT count and the amount of radioactivity was determined. The total injected dose in each patient was calculated by the difference between the radioactivities of the syringe before and after injection. The average SPECT count in a region of interest was divided by the total injected dose after conversion from MBq to counts by means of the cross calibration factor. For the delayed image the value was again corrected for the size and decay of the region of interest. To estimate the MIBG concentration per unit of blood flow the uptake ratio MIBG:thallium was calculated from the corrected uptake. The clearance rate of MIBG (washout rate) was calculated as (early uptake − delayed uptake) ÷ early uptake in each segment from the regions of interest on transaxial images. These analyses were performed on the septum, generally the most hypertrophic region, and on the apical portion.

Visual evaluation of the presence or absence of defects in the MIBG SPECT images was performed in the following way to minimise bias in interpretation. A group of cardiologists determined the most hypertrophic region from the ventriculographic and echocardiographic findings. Sites of MIBG defects were determined in the delayed MIBG images by two nuclear medicine experts who were unaware of the ventriculographic and echocardiographic findings. Finally the two sets of results were combined.

ECHOCARDIOGRAPHY

Cross sectional echocardiographic studies that comprised long axis, short axis, and apical four chamber views were performed within one week of the radionuclide studies in all patients. The hypertrophied sites were identified and the thickness of the septum and posterior wall of the left ventricle was measured.

STATISTICAL ANALYSIS

All data are expressed as mean (1 SD). The significance of the variance of the means was determined by Student's t test. The presence of MIBG defects was assessed by the χ^2 test. Differences were considered statistically significant at $p < 0·05$.

Results

There was no significant age difference between the two groups (50·1 (11·4) for group A and 59·4 (7·3) for group B). Also the thickness of the left ventricular wall did not differ significantly between the two groups (interventricular septal thickness 16·3 (3·4) mm and 18·3 (2·0) mm, left ventricular posterior wall thickness 12·1 (3·0) mm and 10·7 (2·9) mm in groups A and B respectively).

ELECTROCARDIOGRAPHIC CHANGES AND MIBG DEFECTS

The table shows the serial electrocardiographic changes, hypertrophied sites, and MIBG defect sites. Mean follow up was 45 (range 12–143) months. In group A the electrocardiographic changes consisted of further deepening of the negative T wave in one patient and no change in the other 14. By contrast, in group B the negative T wave decreased in four patients including one patient in whom it disappeared. The results for the remaining three patients were complicated by conduction system disturbances consisting of atrial fibrillation, right bundle branch block, and sick sinus syndrome in one case each. Defects in MIBG uptake were found in only one of the 15 patients of group A but in six of the seven patients in group B ($p < 0·005$), the one remaining patient in group B had a thallium scan defect in the hypertrophied interventricular septum. The MIBG defect sites were mostly at the sites of wall hypertrophy (table).

Electrocardiographic changes, sites of wall hypertrophy, and MIBG defects

Patient (age) sex	*ECG change*	*Hypertrophy*	*MIBG defect*
Group A:			
1 (45) M	LVH NT → NT↑	AS	
2 (53) F	LVH → NC	ALL	
3 (63) M	LVH NT → NC	AS	
4 (69) M	LVH GNT → NC	AS,Ap	
5 (28) M	LVH NT → NT↑	Ap	
6 (54) M	LVH NT → NC	AS, Ap	
7 (44) M	LVH GNT → NC	AS	
8 (40) M	LVH NT → NT	AS, Ap	
9 (54) M	h-R NT → NC	S	
10 (67) F	LVH → NC	AS, Ap	A, Ap
11 (53) F	LVH → NC	AS	
12 (39) M	LVH NT → NC	Ap	
13 (48) M	LVH NT → NC	AS, Ap	
14 (56) F	LVH → NC	AS	
15 (38) M	LVH NT → NC	AS	
Group B:			
1 (69) M	LVH GNT → NT↓	AS, Ap	Ap
2 (57) F	LVH NT → Af	AS	
3 (66) M	LVH GNT → NT↓	AS, Ap	AS, Ap, I
4 (63) M	LVH GNT → NT↓	AS, Ap	AS, Ap, I
5 (58) F	LVH RBBB QS → NC	AS	S
6 (47) M	LVH GNT → NT↓	AS, Ap	Ap
7 (56) F	LVH SSS → NC	S, I	S, I

ECG, electrocardiogram; LVH, left ventricular hypertrophy; NT, negative T wave (less than −1·0 mV) in precordial leads; GNT, giant negative T wave (more than −1·0 mV) in precordial leads; NT↑ increased negative T wave; NT↓, decrease or disappearance of negative T wave; h-R, high R wave in right precordial leads; RBBB, right bundle branch block; QS, QS pattern in anterior precordial leads; SSS, sick sinus syndrome; Af, atrial fibrillation; NC, no change; ALL, global hypertrophy of left ventricle; AS, anteroseptal wall; A, anterior wall; S, interventricular septum; Ap, apex; I, inferior wall.

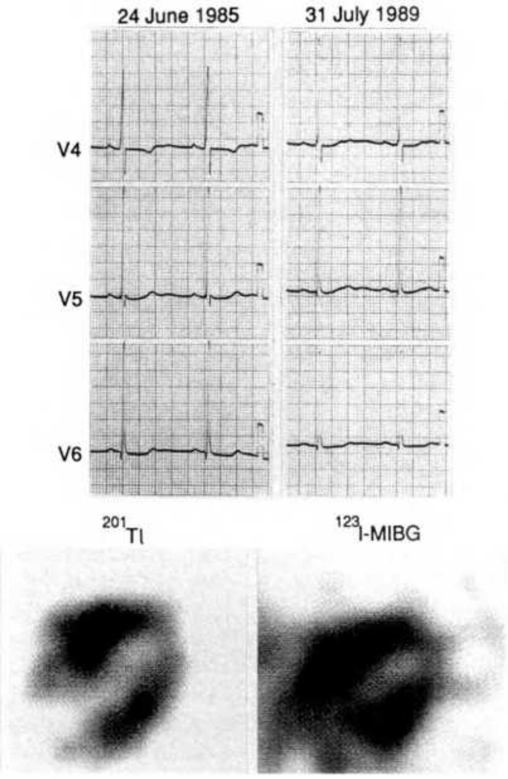

Figure 1 Electrocardiograms from a patient in group A showing slight T wave changes between the electrocardiograms. Increased accumulation, predominantly in the interventricular septum, was found on both the thallium image and MIBG image.

EARLY UPTAKE AND CLEARANCE OF MIBG

EXAMPLES OF ACTUAL CASES

Figure 1 shows the results for one patient in group A, a 53 year old woman. Only slight T wave changes occurred between the 1985 and 1989 electrocardiograms. On the thallium image increased accumulation occurred predominantly in the interventricular septum; increased accumulation at the same site on the MIBG image. Figure 2 shows the results for one patient in group B, a 66 year old man. A giant negative T wave of >1·0 mV was found on the 1977 electrocardiogram. This had disappeared on the 1989 electrocardiogram. On the thallium image increased accumulation was found predominantly in the apex whereas on the MIBG image defects were found from the apex to inferior wall and part of the anterior wall.

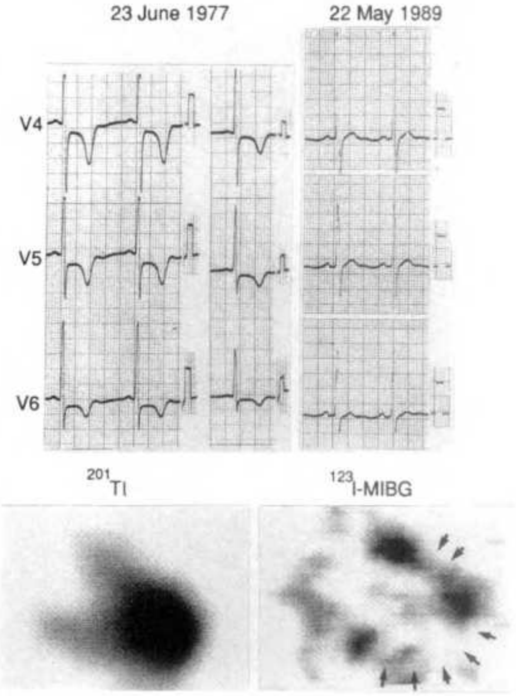

Figure 2 Electrocardiograms from a patient in group B showing that the giant negative T wave had disappeared from the second electrocardiogram. On the thallium image increased accumulation was found predominantly in the apex. On the MIBG image defects were found in the apex, inferior wall, and anterior wall (arrows).

EARLY UPTAKE AND CLEARANCE OF MIBG

There was no difference in early uptake (MIBG : thallium) between the two groups (0·57 (0·17) for group A and 0·58 (0·20) for group B). By contrast, MIBG clearance was significantly greater in group B (0·25 (0·17) *v* 0·10 (0·15)) (fig 3).

Discussion

Disproportionate hypertrophy of the left ventricle is a characteristic feature of hypertrophic cardiomyopathy, the clinical course of which is extremely variable. In 1979 Cate and Roelandt reported on two adult patients with hypertrophic obstructive cardiomyopathy who showed left ventricular dilatation.[1] Subsequently, there have been several reports of patients with hypertrophic cardiomyopathy undergoing transition to a dilated cardiomyopathy-like disease over a course of three to 17 years.[2 3 8] Spirito *et al* investigated 217 patients with hypertrophic cardiomyopathy and reported left ventricular systolic dysfunction in about 10%.[9] Also patients with a poor left ventricular ejection fraction also had left

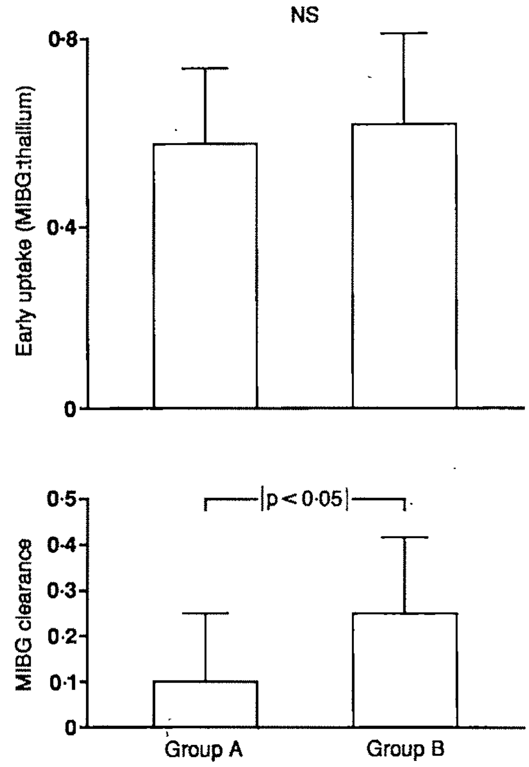

Figure 3 Early uptake and MIBG clearance in the two groups. There was no difference in early uptake between the two groups but clearance of MIBG was significantly greater in group B.

ventricular wall thinning and cavity enlargement. Nagata *et al* in a study of patients with familial hypertrophic cardiomyopathy found that older patients show dilatation or diminished contraction of the left ventricle more frequently than younger patients.[10] None the less, transition to dilated cardiomyopathy has been reported in children.[2] Necrosis due to narrowing of the small coronary arteries, progression of fibrosis, and disarray have all been implicated as causes of the change from hypertrophic cardiomyopathy to dilated cardiomyopathy in studies of endomyocardial biopsies and histological examination at necropsy.[3 11 12] It is not known how regional myocardial sympathetic nerve activity changes in association with these histological changes and myocardial systolic dysfunction.

Because the effects of MIBG are similar to those of noradrenaline, is a promising indicator of regional sympathetic nerve activity and is already used as a sympathetic nervous system imaging agent in the diagnosis of disorders such as pheochromocytoma.[13–15] Recently it has been reported that MIBG accumulates in the heart as well as the adrenal medulla, and it is attracting attention as a useful indicator of cardiac sympathetic nerve activity. Despite experimental evidence that catecholamines are involved in the aetiology of hypertrophic cardiomyopathy,[16] there have been few reports of sympathetic nerve imaging in this condition.

We used MIBG to evaluate the correlation between sympathetic nerve function in the heart and the pathophysiological changes that occur in hypertrophic cardiomyopathy. Transport of MIBG to the tissues is dependent on blood flow. In hypertrophic cardiomyopathy the small coronary arteries are narrowed,[17 18] and diminished coronary flow reserve[19 20] and perfusion abnormalities have been shown by thallium myocardial scintigraphy.[21 22] To correct for the influence of these blood flow abnormalities, MIBG uptake was expressed as a ratio to thallium uptake imaged under the same conditions. At the time of visual evaluation, we judged as abnormal only those sites that showed adequate thallium accumulation together with decreased MIBG accumulation or defects; we excluded patients that showed defects on the thallium image. Because at that time there were no established quantitative nuclear medicine techniques to correct for scatter and absorption such correction was not attempted. Thus correction factors were not a source of error when the uptake ratio MIBG: thallium was calculated.

The electrocardiographic course in 100 patients with hypertrophic cardiomyopathy was assessed by McKenna *et al*; follow up results showed increased voltage in most and reduced voltage in only four patients.[23] We previously reported in a study of patients with hypertrophic cardiomyopathy in whom left ventriculography was performed more than twice that T wave changes on the electrocardiograms more sensitively expressed the pathophysiological changes of hypertrophic cardiomyopathy than did the differences in voltage (SV1 + RV5).[4] In cases showing inversion of a positive T wave or increase of a negative T wave, left ventricular wall hypertrophy progressed. Conversely, in cases in which a negative T wave decreased or disappeared, left ventricular systolic function was depressed with wall thinning, particularly of the apical portion. A defect in MIBG uptake was found in the hypertrophied site in only one case in group A. This extended from the anterior of the left ventricle to the apical portion. By contrast, in six of the seven patients in group B in whom a negative T wave decreased or in whom conduction system disturbances were found, MIBG defects centred roughly on the site of hypertrophy in the ventricle and in the one remaining patient, both thallium and MIBG defects were found in the hypertrophied site. We speculate that a decrease in the negative T wave is brought about by primary changes such as aggravated ischaemia due to progressive impairment of the microcirculation and increased stress in association with dilatation of the left ventricular chamber. Secondary changes due to a reduction in voltage after myocyte degeneration and necrosis and left ventricular wall thinning as well as interventricular conduction disturbances may also play a part. A decrease in the negative T wave was found in four of the seven patients in group B, although this was accompanied by a decrease in the R wave in only two of these patients. This suggests that decreases in the negative T wave and R wave are not necessarily associated. Also, findings that suggested worsening of conduction disturbances, such as prolongation of the QRS interval, were not found in any patient. This suggests that this decrease in the negative T wave does not have a single cause, but is the result of various factors such as myocyte degeneration and necrosis and aggravation of ischaemia leading to the development of myocardial interstitial fibrosis and changes in cardiac sympathetic nerve distribution—these are indicated by the MIBG defects. The possibility that primary abnormalities of the cardiac sympathetic nerves influence the myocytes and result in T wave changes, cannot however, be excluded.

To evaluate the MIBG uptake per unit of blood flow, the MIBG : thallium ratios from the regions of interest were examined. No difference in early uptake between the two groups was found, but MIBG clearance was greater in group B. Henderson *et al* studied 16 patients with congestive cardiomyopathy and reported that the distribution of MIBG activity within the myocardial images showed significantly greater heterogeneity in the congestive cardiomyopathy group than in the controls.[24] This is consistent with the results of our group B. It is thought that a major component of the myocardial retention of MIBG is sequestration within the noradrenaline storage vesicles of the adrenergic nerves.[5] Nakajo *et al* in a study of the rat heart reported that intravesicular accumulation was relatively uniform, with a plateau reached about four hours after intravenous injection, whereas extravesicular accumulation rapidly decreased from five minutes to six hours after injection.[25] They also studied MIBG movement, distinguishing between intravesicular and extravesicular sites. So there are two explanations why early uptake does not differ between the two groups though clearance is greater in group B. One possibility is that in group B there are few storage vesicles in the cardiac sympathetic nerve endings and so changes in extravesicular accumulation of MIBG play a major part, with a large MIBG clearance as a result. The second possibility is that in group B MIBG turnover is enhanced. According to the report of Glowniak *et al*, uptake of MIBG in the transplanted heart, amounts to less than 10% of the uptake in controls.[26] So an enhanced MIBG turnover seems more likely. Because cardiac function was more often depressed in group B than in group A we think that myocardial necrosis and scarring developed owing to increased disarray and fibrosis and this led to abnormalities of regional sympathetic nerve distribution. These abnormalities coupled with diminished systolic force enhance cardiac sympathetic nerve activity and noradrenaline turnover. Kawai *et al* reported that intramyocardial noradrenaline was reduced in dilated cardiomyopathy.[27] We believe that as with the disease progressed cardiac noradrenaline was further reduced leading to a reduction of MIBG uptake and that ischaemia due to narrowing of the intramyocardial small coronary arteries and increased fibrosis resulted in considerably depressed cardiac function and in thallium defects. Recently, reports that mutations in the cardiac myosin heavy chain genes are present in patients with familial hypertrophic cardiomyopathy[28 29] have been attracting attention. On the other hand, Weber *et al* reported that structural remodelling of collagen, which is the extracellular matrix of the myocardium occurs in left ventricular hypertrophy.[30]

How are these abnormalities related to the lack of sympathetic homogeneity found in the hearts of patients with hypertrophic cardiomyopathy? Clarification of this point awaits the results of future studies. Data on normal subjects would be of interest, but because this study was conducted as part of a clinical trial, it was limited to patients with hypertrophic cardiomyopathy. Patients in group B were studied for longer than patients in group A (72 (44) *v* 32 (16) months). Further studies are needed to determine whether these changes occur in patients with hypertrophic cardiomyopathy during a long follow up period and to determine the relations between these changes, progression of the disease process, and prognosis.

1 ten Cate FJ, Roelandt J. Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. *Am Heart J* 1979;**97**:762–5.
2 Beder SD, Gutgesell HP, Mullins CE, McNamara DG. Progression from hypertrophic obstructive cardiomyopathy to congestive cardiomyopathy in a child. *Am Heart J* 1982;**104**:155–6.
3 Fujiwara H, Onodera T, Tanaka M, Shirane H, Kato H, Yoshikawa J, *et al*. Progression from hypertrophic obstructive cardiomyopathy to typical dilated cardiomyopathy-like features in the end stage. *Jpn Circ J* 1984;**48**:1210–4.
4 Horita Y, Genda A, Shimizu M, Sugihara N, Suematsu T, Kita Y, *et al*. Serial electrocardiographic and angiographic changes of patients with hypertrophic cardiomyopathy. *Jpn Circ J* 1989;**53**:1327–42.
5 Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu J, Clinthorne NH, *et al*. Myocardial imaging with a radio-iodinated norepinephrine storage analog. *J Nucl Med* 1981;**22**:22–31.
6 Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, *et al*. Myocardial imaging in man with I-123 meta-iodobenzyl-guanidine. *J Nucl Med* 1981;**22**:129–32.
7 Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, *et al*. Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. *J Nucl Med* 1987;**28**:1625–36.
8 Funakoshi M, Imamura M, Sasaki J, Fujino M, Kawano T, Sasaki Y, *et al*. Seventeen year follow-up of a patient with hypertrophic cardiomyopathy which progressed to dilated cardiomyopathy. *Jpn Heart J* 1984;**25**:805–9.
9 Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. *Am J Cardiol* 1987;**59**:123–9.
10 Nagata S, Park Y, Minamikawa T, Yutani C, Kamiya T, Nishimura T, *et al*. Thallium perfusion and cardiac enzyme abnormalities in patients with familial hypertrophic cardiomyopathy. *Am Heart J* 1985;**109**:1317–22.
11 Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol* 1979;**43**:1086–102.
12 Yutani C, Imakita M, Ishibashi-Ueda H, Hatanaka K, Nagata S, Sakakibara H, *et al*. Three autopsy cases of progression to left ventricular dilatation in patients with hypertrophic cardiomyopathy. *Am Heart J* 1985;**109**:545–53.
13 Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with (^{131}I) iodobenzylguanidine. *J Nucl Med* 1980;**21**:349–53.
14 Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, *et al*. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 1981;**305**:12–7.
15 Valk TW, Frager MS, Gross MD, Sisson JC, Wieland DM, Swanson DP, *et al*. Spectrum of pheochromocytoma in multiple endocrine neoplasia. A scintigraphic portrayal using ^{131}I-metaiodobenzylguanidine. *Ann Intern Med* 1981;**94**:762–7.
16 Sole MJ, Lo C, Laird CW, Sonnenblick EH, Wurtman RJ. Norepinephrine turnover in the heart and spleen of the cardiomyopathic Syrian hamster. *Circ Res* 1975;**37**:855–62.
17 Campbell M, Summerell JM, Bras G, Hayes JA, Stuart KL. Pathology of idiopathic cardiomegaly in Jamaica. *Br Heart J* 1971;**33**:193–202.
18 James TN, Marshall TK, De Subitaneis Mortibus. XII. Asymmetrical hypertrophy of the heart. *Circulation* 1975;**51**:1149–66.
19 Thompson DS, Naqvi N, Juul SM, Swanton RH, Coltart

DJ, Jenkins BS, *et al.* Effects of propranolol on myocardial oxygen consumption, substrate extraction, and haemodynamics in hypertrophic obstructive cardiomyopathy. *Br Heart J* 1980;44:488–98.

20 Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa G. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. *Circulation* 1982;65:778–89.

21 Pitcher D, Wainwright R, Maisey M, Curry P, Sowton E. Assessment of chest pain in hypertrophic cardiomyopathy using exercise thallium-201 myocardial scintigraphy. *Br Heart J* 1980;44:650–6.

22 O'gara PT, Bonow RO, Maron BJ, Damske BA, Lingen AV, Bacharach SL, *et al.* Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* 1987;76:1214–23.

23 McKenna WJ, Borggrefe M, England D, Deanfield J, Oakley CM, Goodwin JF. The natural history of left ventricular hypertrophy in hypertrophic cardiomyopathy: an electrocardiographic study. *Circulation* 1982;66:1233–40.

24 Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, *et al.* Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation* 1988;78:1192–9.

25 Nakajo M, Shimabukuro K, Yoshimura H, Yonekura R, Nakabeppu Y, Tanoue P, *et al.* Iodine-131 metaiodobenzylguanidine intra- and extra-vesicular accumulation in the rat heart. *J Nucl Med* 1986;27:84–9.

26 Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC. Woodward WR. Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med* 1989;30:1182–91.

27 Kawai C, Yui Y, Hoshino T, Sasayama S, Matsumori A. Myocardial catecholamines in hypertrophic and dilated (congestive) cardiomyopathy: a biopsy study. *J Am Coll Cardiol* 1983;2:834–40.

28 Tanigawa G, Jarcho JA, Kass S, Solomon SD, Vosberg H, Seidman JG, *et al.* A molecular basis for familial hypertrophic cardiomyopathy: an α/β cardiac myosin heavy chain hybrid gene. *Cell* 1990;62:991–8.

29 Geisterfer-Lowrance AAT, Kass S, Tanigawa G, Vosberg H, McKenna W, Seidman CE, *et al.* A molecular basis for familial hypertrophic cardiomyopathy: a β cardiac myosin heavy chain gene missense mutation. *Cell* 1990;62: 999–1006.

30 Weber KT, Janicki JS, Shroff SG, Pick P, Chen RM, Bashey RI. Collagen remodeling of the pressure-overloaded, hypertrophied nonhuman primate myocardium. *Circ Res* 1988;62:757–65.

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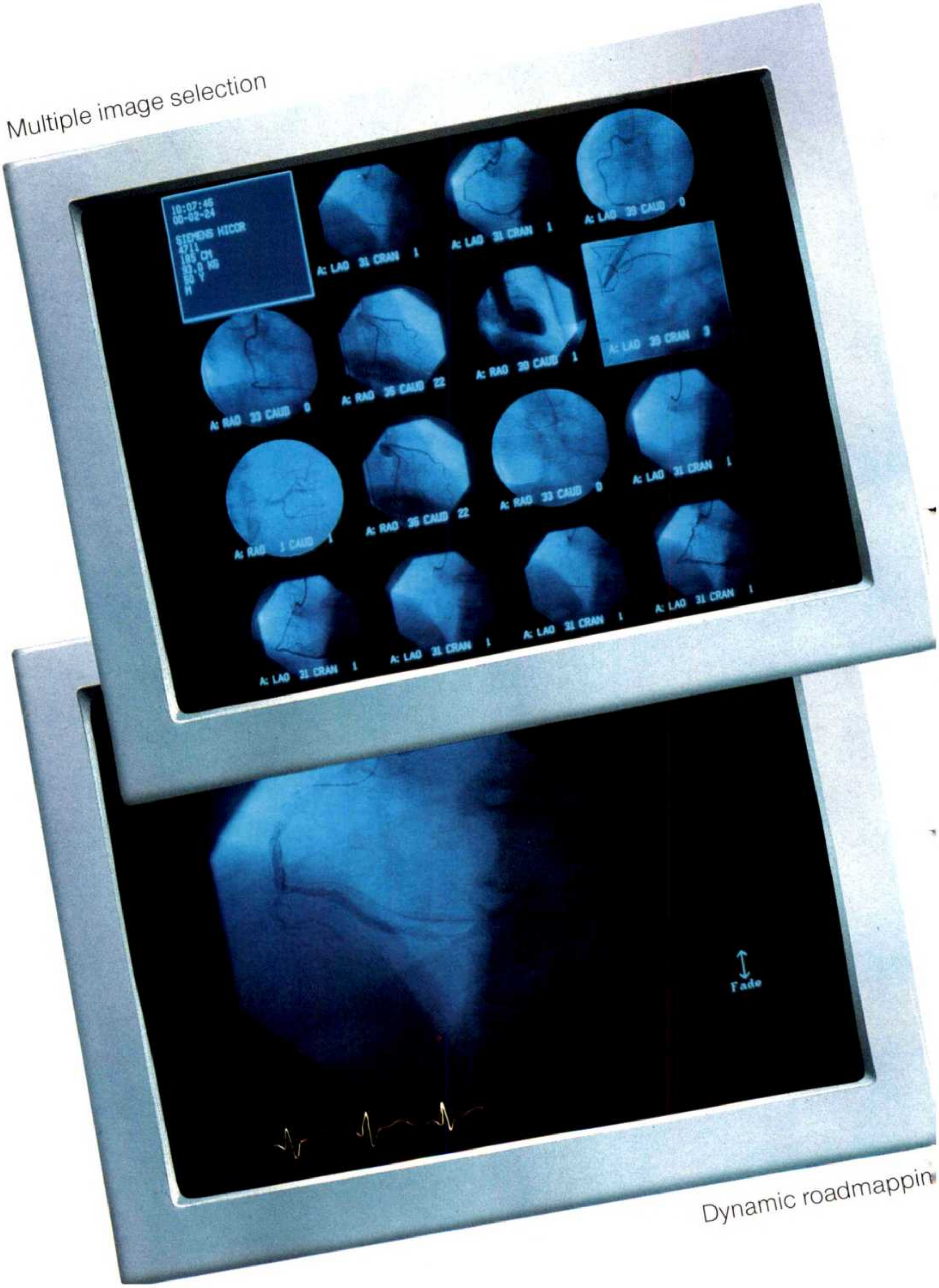

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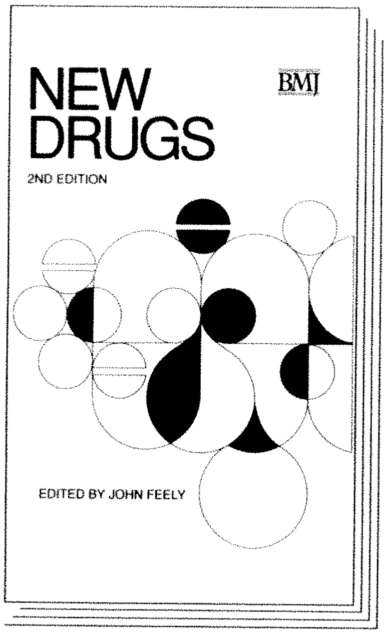

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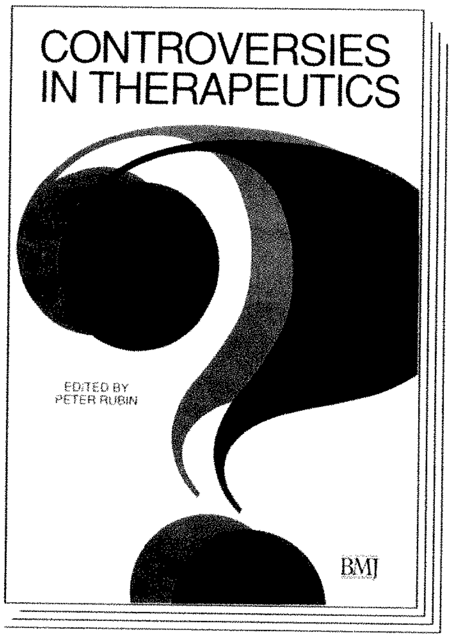

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Myocardial oxygen consumption in aortic valve disease with and without left ventricular dysfunction

Juerg Schwitter, Franz R Eberli, Manfred Ritter, Marko Turina, Hans P Krayenbuehl

Abstract

***Objective*—To assess whether and to what extent myocardial oxygen consumption is modified by hypertrophy and alterations in contractility in patients with aortic valve disease and to evaluate the influence of regression of left ventricular hypertrophy and improvement of contractility on myocardial oxygen consumption after successful aortic valve replacement.**

***Design*—A cohort analytical study to investigate the influence of the "explanatory" variables of myocardial oxygen consumption by multiple regression analysis. A comparison of myocardial oxygen consumption in preoperative patients with that after operation in a group with comparable severity of aortic valve disease before operation (analysis of covariance).**

***Patients*—In six controls and in 43 patients with aortic valve disease and normal coronary arteries standard haemodynamic variables were measured, left ventricular biplane cineangiography performed, and coronary sinus blood flow measured by thermodilution. The patients were divided into three groups: 19 preoperative patients with normal ejection fraction (≥57%) (group 1); nine preoperative patients with reduced ejection fraction (<57%) (group 2); 16 postoperative patients (one with preoperative and postoperative measurements (group 3). Postoperative evaluation was performed 12–51 months after surgery.**

***Main outcome measurements*—Myocardial oxygen consumption/100 g left ventricular muscle mass and its suspected "explanatory" variables—that is, peak systolic left ventricular circumferential wall stress, heart rate, contractility (assessed by left ventricular ejection fraction), and left ventricular muscle mass index.**

***Results*—Multiple regression analysis showed that the product of peak systolic stress and heart rate ($p < 0.0001$) and ejection fraction ($p < 0.03$) were positively correlated with myocardial oxygen consumption/100 g and that left ventricular muscle mass index ($p < 0.002$) was negatively correlated with myocardial oxygen consumption/100 g ($r = 0.72$; $n = 50$ measurements). Myocardial oxygen consumption per 100 g at a given stress-rate product was higher in the controls than in group 1 (hypertrophied ventricles with normal ejection fraction) and was also higher in group 1 than in group 2 (hypertrophied ventricles with reduced ejection fraction). In a subgroup of the postoperative patients with complete regression of hypertrophy and normalisation of contractility, myocardial oxygen consumption per 100 g at a given stress-rate product was indistinguishable from that in controls.**

***Conclusions*—When the actual stress-rate product was used as an index of overall left ventricular performance the results suggested that mechanical efficiency was increased in hypertrophied ventricles especially when contractility was decreased. These changes in mechanical efficiency seemed to be reversible during the postoperative course when muscle mass and contractility returned to normal.**

The oxygen consumption of the human heart depends upon various factors—mainly systolic tension development or systolic wall stress, heart rate, and contractility.[1-3] Of lesser importance are the oxygen costs associated with shortening and the basal resting metabolism.[3] These determinants of myocardial oxygen consumption are valid for the normal heart at rest and during acute changes of loading or inotropism. But it is not known whether and to what extent the degree and appropriateness of ventricular hypertrophy and myocardial contractility, or both, influence and modify the relations between the myocardial oxygen consumption and its classic determinants in the chronically overloaded heart. Earlier studies showed alterations in coronary blood flow and the myocardial oxygen consumption in cardiac hypertrophy, but many of these studies involved animal models.[4-6] The present study was performed in patients in whom left ventricular hypertrophy had developed in response to the long-standing haemodynamic burden of isolated aortic stenosis or insufficiency or a combined lesion. The patient population was divided into two groups—one with left ventricular dysfunction and one without. We also examined a third group of patients with regression of cardiac hypertrophy 26 months after successful aortic valve replacement.

The three objectives of the present investigation were to evaluate the influence of loading

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conditions (represented by the product of heart rate and peak systolic stress (stress-rate product)) on myocardial oxygen consumption per 100 g in hypertrophied hearts compared with the normal heart; to assess the influence of cardiac contractility on myocardial oxygen consumption per 100 g; and to evaluate whether the postoperative regression of left ventricular hypertrophy modified the relation between the myocardial oxygen consumption per 100 g and its haemodynamic determinants.

Patients and methods

PATIENTS

Six patients (four men and two women) with normal left ventricular function who underwent left heart catheterisation for atypical chest pain and had no coronary artery disease served as controls. Coronary flow reserve after dipyridamole was determined by thermodilution and was normal in all of them (range 2·18–4·30, mean (SD) 2·9 (0·9): normal values 1·74–4·30, 2·54 (1·02))[7]. None of the controls was being treated with drugs or had a history of arterial hypertension; values of fasting plasma glucose and cholesterol were in the normal range.

Thirty patients (21 men, nine women; mean (SD) age 61 (7) years) had aortic stenosis and were in New York Heart Association (NYHA) class 2·2 (SD 0·4). The mean (SD) systolic pressure gradient across the aortic valve was 71 (16) mm Hg. The mean (SD) aortic valve area was 0·7 (0·17) cm^2, range 0·3–1·0 cm^2 (including six patients with combined aortic valve disease and predominant aortic stenosis defined as aortic valve area $\leqslant 1{\cdot}0$ cm^2). Thirteen patients, all men, (age 51 (8) years) had aortic insufficiency and were in NYHA class 2·0 (SD 0·4). The mean (SD) aortic regurgitation fraction determined by thermodilution was 54 (10)% (range 37–75%). Three of the 13 patients had combined aortic valve disease with predominant insufficiency defined as aortic valve area $> 1{\cdot}0$ cm^2. All patients had normal coronary arteries by selective coronary arteriography.

Twenty eight of the 43 patients with aortic valve disease were studied preoperatively. In four of the six controls and in the 16 postoperative patients measurements of coronary sinus blood flow and myocardial oxygen consumption were performed at an ambulatory right heart catheterisation. One patient was studied both before and after operation.

PATIENT GROUPS

Patients were divided in groups as follows: *controls*, six, with normal ejection fraction ($\geqslant$57%)[8]; *group 1*, 19 patients with aortic stenosis or insufficiency and normal ejection fraction; *group 2*, nine patients with aortic stenosis or insufficiency and reduced ejection fraction (<57%); *group 3*, 16 patients after successful aortic valve replacement for aortic stenosis or insufficiency. Group 3 was further divided into: *group 3A*, six patients with complete postoperative regression of left ventricular hypertrophy (normal left ventricular muscle mass index $\leqslant$117 g/m^2 [9]) and an ejection fraction within the range for the controls (63–77%); and *group 3B*, 10 patients with incomplete regression of left ventricular hypertrophy (left ventricular muscle mass index >117 g/m^2, n = 4) and/or an ejection fraction in the low normal range (57–62%, n = 6). Group 2 patients were considered to have depressed contractility because their ejection fraction was reduced in the presence of an afterload and preload that were not different from those in the controls.

Patients in groups 1, 2, and 3 in the preoperative state did not differ with regard to the NYHA class (table 1). In group 3 two of 16 patients had mild dyspnoea during exercise (NYHA class I–II). In group 1 two patients were taking digitalis, two nitrates, two angiotensin converting enzyme inhibitors, one diuretics, and one calcium antagonists. In group 2 three patients were taking digitalis, three diuretics, three calcium antagonists, and two nitrates. In group 3 five patients were taking calcium antagonists, two digitalis, and two diuretics. All drugs were stopped at least 24 hours before catheterisation.

CATHETERISATION AND CINEANGIOGRAPHY

The controls and all 43 preoperative patients underwent right and left heart catheterisation in the fasting state. Informed consent was obtained from all patients. Premedication consisted of oral chlordiazepoxide (10 mg) administered an hour before the procedure. Right sided pressures and the aortic pressure were measured with a 7F Cournand catheter and a fluid filled 8F pigtail catheter respectively. In patients with aortic valve disease left ventricular pressure was obtained via a transseptally inserted 8·5F Brockenbrough catheter. A peripheral lead of the electrocardiogram was recorded at the same time as the pressures. Left ventricular cineangiography was performed in the right (30°) and left (60°) anterior oblique projections.

Biplane left ventricular volumes were determined according to the area-length method.[10] Left ventricular end diastolic wall thickness (cm), muscle mass (g), and muscle mass index (g/m^2) were measured according to the technique of Rackley *et al.*[11] The left ventricular end diastolic circumferential wall stress was calculated according to the formula of Sandler and Dodge.[12] Peak systolic wall stress (S_{peak}) was estimated at a point one third through ejection as proposed by Gaasch *et al.*[13] In the 16 postoperative patients (group 3) an ambulatory right heart catheterisation was performed. A 8F pigtail catheter was inserted into the pulmonary artery. Biplane left ventricular angiograms were obtained after injection of 50–60 ml of Iopamiro 370 (iopamidol and trometamol) into the pulmonary artery. In these 16 postoperative patients and in four controls in whom ambulatory coronary sinus blood flow was measured 7–17 days after diagnostic coronary arteriography left ventricular end diastolic pressure was replaced by mean pulmonary wedge pressure, left ventricular

tricular systolic pressure was taken as systolic cuff pressure, and mean aortic pressure was calculated as diastolic cuff pressure plus one third of the pulse pressure amplitude. In the postoperative patients the pressure gradient across the aortic valve prosthesis was ignored.

CORONARY BLOOD FLOW MEASUREMENTS

Coronary sinus blood flow was measured after the diagnostic catheterisation in 28 preoperative patients with aortic valve disease and in two controls. In four controls and the 16 postoperative patients (one of whom had both preoperative and postoperative evaluation) measurement of coronary sinus blood flow was performed on an ambulatory basis with right heart catheterisation—in the postoperative patients this was a mean of 26 months (range 12–52 months) after successful aortic valve replacement. Total coronary sinus outflow was measured by the coronary sinus thermodilution technique.[7 14] A 7F thermodilution catheter (CCS-7U-90A or B, Webster Laboratory, Altadena, California) was introduced from the right femoral vein or in a few cases from the right cubital vein and advanced into the coronary sinus and the dilution thermistor was placed 2 cm from the orifice. The position was checked by injection of small amounts of contrast dye. Injection of cold saline into the superior vena cava did not change the temperature curve of the thermistor in the coronary sinus.[15] The signals of the external (mixing temperature of blood and saline) and internal (temperature of the injected saline) thermistors were recorded on a oscillograph (Electronics for Medicine VR-12) at a paper speed of 5 mm/s. Saline at room temperature was infused through the thermodilution catheter at a rate of 50 ml/min and coronary sinus blood flow (ml/min) was calculated according to the formula of Ganz *et al.*[14] Coronary resistance (CR) (mm Hg-min ml^{-1}) was calculated according to the following equation:

$$CR = \frac{MAP - CSP}{CSBF}$$

where MAP equals mean aortic pressure (mm Hg); CSP, mean coronary sinus pressure (mm Hg); and CSBF, coronary sinus blood flow (ml/min). Arterial and coronary sinus oxygen saturation were measured by an Instrumentation Laboratory System 1302 blood gas analyser (Nanolab AG, CH-Schlieren). Myocardial oxygen consumption (ml/min) was determined as the product of the arteriocoronary sinus oxygen difference (vol%) and the coronary sinus blood flow. Coronary sinus blood flow, coronary resistance, and the myocardial oxygen consumption were standardised for 100 g of left ventricular muscle mass. Because injection of contrast can alter coronary dynamics,[16] coronary sinus blood flow was not recorded within 20 minutes of an injection of contrast agent.

In controls coronary sinus outflow was determined at rest as well as after infusion of dipyridamole (0·5 mg/kg body weight) over 15 minutes. The coronary flow ratio (coronary flow reserve) was calculated as coronary sinus blood flow after dipyridamole infusion divided by the blood flow at rest.[7]

STATISTICAL ANALYSIS

We used a one way analysis of variance to compare data from the controls and the patients from groups 1, 2, and 3. If the analysis showed an overall significant p value ($p < 0·05$) we used Scheffe's test to compare all pairs of means. When only two groups were compared we used the unpaired Student's *t* test. Comparisons between pre and post operative data for group 3 patients were performed by the paired Student's *t* test.

Initially differences in myocardial oxygen consumption between the four groups were compared by analysis of covariance[17] with the stress-rate product as a covariate, using the correction for multiple tests by Bonferroni. In a second step "explanatory" variables were regarded as continuous rather than categorical and multiple regressions were performed. In all tables values are given as mean (SD).

Results

The four patient groups did not differ in age (49, 59, 58, 57 years) and body surface area (1·86, 1·79, 1·82, 1·90 m^2). None of the patients was anaemic and the haemoglobin concentration was similar in the four groups.

HAEMODYNAMICS AND ANGIOGRAPHIC DATA IN PREOPERATIVE PATIENTS AND CONTROLS (TABLES 1 AND 2)

In the preoperative patients with predominant aortic stenosis and left ventricular dysfunction (subset of group 2) the aortic valve area was slightly smaller ($p < 0·05$) than in the patients without left ventricular dysfunction (subset of group 1). The mean aortic pressure gradient was similar.

The left ventricular muscle mass index was higher in the preoperative patients with left ventricular dysfunction (group 2) and without (group 1) than in the controls and the postoperative patients (group 3). The left ventricular end diastolic wall thickness was similar in patients in groups 1 and 2 but it was higher than in the controls and group 3. The left ventricular end diastolic volume index in group 2 was larger than in the controls and postoperative patients; there was no difference between patients in groups 1 and 2. Left ventricular systolic pressure was higher in groups 1 and 2 than in the controls. In the postoperative patients left ventricular end diastolic pressure was lower than in the groups 1 and 2 patients but did not differ from that in the controls. There was no difference in peak systolic stress between controls and patients with aortic valve disease with left ventricular dysfunction and without. Peak systolic stress was lower in the postoperative group than in groups 1 and 2. The end diastolic circumferential stress was higher in the group 2 patients than in groups 1 and 3. The cardiac index was lower in group 2 than in the controls.

Table 1 Preoperative data for groups 1, 2, and 3

Group	n	Age (y) (mean (SD) (range))	NYHA class (mean (SD) (range))	Mean AV gradient (mm Hg) (mean (SD) range))	AVA (cm²) (mean (SD) range))	f_{ar} (%) (mean (SD) range))	f_{mr}‡ (%) (mean (SD) range))
Controls	6	49 (10) (30–58)	—	—	—	—	—
Group 1:							
AS	16	61 (6) (49–73)	2·1 (0·4) (1·5–3)	73 (16) (39–96)	0·73 (0·14) (0·5–1·0)	2/16†	4/16
AI	3	46 (8) (39–54)	1·8 (0·3) (1·5–2)	2/3*	2/3*	56 (6) (46–65)	0/3
Group 2:							
AS	5	62 (8) (52–72)	2·3 (0·4) (2–3)	71 (21) (38–93)	0·54 (0·17) (0·3–0·7)	2/5†	3/5
AI	4	52 (11) (36–62)	2·3 (0·5) (2–3)	1/4*	1/4*	64 (8) (58–75)	0/4
Group 3:							
AS	10	58 (9) (39–69)	2·3 (0·4) (2–3)	69 (12) (54–97)	0·76 (0·19) (0·5–1·0)	2/10†	4/10§
AI	6	54 (6) (46–58)	2·2 (0·5) (1·5–3)	0/6*	0/6*	51 (6) (47–55)	3/6

AI, aortic insufficiency; AS, aortic stenosis; AVA, aortic valve area; f_{ar}: aortic regurgitation fraction; f_{mr}: mitral regurgitation fraction; mean AV gradient, mean aortic valve pressure gradient; NYHA, New York Heart Association.
*Combined aortic valve disease with predominant insufficiency (AVA >1·0 cm²); †combined aortic valve disease with predominant aortic stenosis (AVA ⩽1·0 cm²); ‡mitral insufficiency <15%; §one patient with f_{mr} of 38% (determined by thermodilution).

Table 2 Comparison of haemodynamic and angiographic data (mean (SD)) in controls and patients with aortic valve disease without (group 1) and with (group 2) left ventricular dysfunction and in postoperative patients (group 3)

Group	Number of patients	EF (%)	EDVI (ml/m²)	h_{ed} (cm)	LMMI (g/m²)	LVSP (mm Hg)	Ao_{syst} (mm Hg)	LVEDP (mm Hg)	CI (l/min × m²)	S_{ed} (dyn × 10³/cm²)	S_{peak} (dyn × 10³/cm²)
Controls	6	71 (5)	95 (20)	0·70 (0·07)	77 (14)	117 (18)	122 (10)	10 (3)	4·3 (1·0)	50 (9)	437 (60)
Group 1	19	65 (5)	118 (30)	1·16 (0·11)	163 (42)	207 (37)	138 (21)	14 (4)	3·2 (0·4)	39 (13)	470 (83)
Group 2	9	45 (5)	146 (45)	1·11 (0·17)	170 (42)	170 (54)	124 (17)	20 (11)	2·8 (0·5)	64 (35)	478 (111)
Group 3	16	67 (7)	91 (12)	0·93 (0·13)	100 (18)	133 (19)	133 (19)	7 (4)	3·5 (0·8)	25 (13)	373 (74)
p values:											
Controls v 1		NS	NS	<0·001	<0·001	<0·001	NS	NS	NS	NS	NS
Controls v 2		<0·001	<0·02	<0·001	<0·001	<0·05	NS	<0·05	<0·01	NS	NS
Controls v 3		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
1 v 2		<0·001	NS	NS	NS	NS	NS	NS	NS	<0·02	NS
1 v 3		NS	NS	<0·001	<0·001	<0·001	NS	<0·02	NS	NS	<0·01
2 v 3		<0·001	<0·001	NS	<0·001	NS	NS	<0·001	NS	<0·001	<0·05

Ao_{syst}, systolic aortic pressure; CI, cardiac index; EDVI, left ventricular end diastolic volume index; EF, biplane left ventricular ejection fraction; h_{ed}, end diastolic left ventricular wall thickness; LMMI, left ventricular muscle mass index; LVEDP, left ventricular end diastolic pressure; LVSP, left ventricular systolic pressure; S_{ed}, end diastolic left ventricular circumferential wall stress; S_{peak}, peak systolic left ventricular circumferential wall stress.

CORONARY DYNAMICS IN PREOPERATIVE PATIENTS AND CONTROLS (TABLE 3 AND FIGURES 1 AND 2)

Coronary sinus pressure was similar in the four groups. However, mean aortic pressure and mean coronary perfusion pressure (that is, mean aortic minus mean coronary sinus pressure) in the patients in group 2 (85 and 80 mm Hg) were slightly lower than in the postoperative patients (100 and 97 mm Hg, $p < 0{\cdot}05$). Heart rate was higher in group 2 than groups 1 and 3. There were no differences among the four groups in coronary sinus blood flow, coronary resistance per 100 g muscle mass, haemoglobin concentration, the arteriovenous difference in oxygen content, and the left ventricular oxygen consumption per 100 g muscle mass.

The relation between myocardial oxygen consumption per 100 g and the systolic stress-rate product in controls and in patients in group 1 was compared by regression analysis of covariance. The regression line for group 1 was below that of controls (fig 1). In a second step we considered left ventricular muscle mass index as continuous variable and we performed a multiple regression analysis of the data obtained by pooling controls and patients of group 1 ($n = 25$). In agreement with the result of the covariance analysis the stress-rate product ($p < 0{\cdot}02$) was positively and left ventricular muscle mass index ($p < 0{\cdot}003$) was negatively correlated with the myocardial oxygen consumption per 100 g of myocardium ($r = 0{\cdot}65$). Thus at a given stress-rate product the myocardial oxygen consumption per 100 g of the hypertrophied ventricles with a normal ejection fraction was significantly lower than in non-hypertrophied ventricles with a normal ejection fraction.

When preoperative patients with left ventricular hypertrophy and a preserved ejection fraction (group 1) were compared with patients with a decreased ejection fraction (group 2) regression analysis of covariance showed a regression line for group 1 above that for group 2 (fig 2). When the left ventricular ejection fraction was regarded as a continuous variable in the pooled groups 1 and 2 ($n = 28$), multiple regression analysis showed that the stress-rate product ($p < 0{\cdot}001$) and the ejection fraction ($p < 0{\cdot}03$) were positively correlated with myocardial oxygen consumption per 100 g ($r = 0{\cdot}64$). This indicates a significant reduction in the myocardial oxygen consumption per 100 g at a given stress-rate product in hypertrophied ventricles with reduced contractility compared with hypertrophied ventricles of normal contractility—that is, with a normal ejection fraction.

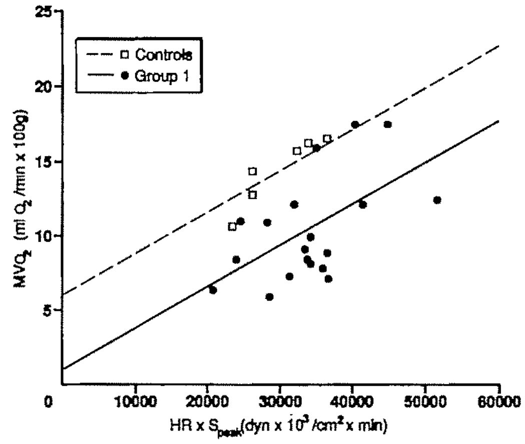
In group 1 the subgroups of patients with aortic stenosis ($n = 16$) and insufficiency ($n = 3$) had similar myocardial oxygen consumptions per 100 g (10·0 (3·3) v 12·3 (4·7) ml

Table 3 A comparison of coronary dynamics (mean (1 SD)) in controls and patients with aortic valve disease without (group 1) and with (group 2) left ventricular dysfunction and in postoperative patients (group 3)

Group	*Number of patients*	*MAP (mm Hg)*	*CSP (mm Hg)*	*HR (beats/min)*	*CSBF/100 g (ml/min × 100 g)*	*CR/100 g (mm Hg × min × 100 g/ml)*	*Hb (g%)*	*AVD-o₂ (vol%)*	*MVo₂/100 g (ml o₂/min)*
Controls	6	98 (8)	4 (1)	69 (11)	120 (18)	0·80 (0·10)	14·2 (0·9)	12·0 (1·1)	14·3 (2·3)
Group 1	19	92 (12)	4 (2·2)	70 (9)*	86 (29)	1·13 (0·36)	13·7 (1·3)	12·2 (1·2)	10·4 (3·5)
Group 2	9	85 (1)	4 (3·0)	83 (12)	79 (31)	1·15 (0·44)	13 8 (1·4)	12·2 (1·5)	9·5 (3·0)
Group 3	16	100 (12)*	3 (1·6)	70 (12)*	91 (39)	1·24 (0·49)	14·4 (0·9)	12·2 (0·8)	11·1 (4·6)

AVD-O_2, arteriocoronary sinus difference in oxygen content; CR/100 g, coronary resistance per 100 g muscle mass; CSBF/100 g, coronary sinus blood flow per 100 g muscle mass; CSP, coronary sinus pressure; Hb, haemoglobin; HR, heart rate; MAP, mean aortic pressure; MVo_2/100 g, myocardial oxygen consumption per 100 g muscle mass.
*$p < 0.05$.

Figure 1 Regression lines (common slope 0·00028 ml O_2 × $cm^2/10^3$ dyn × 100 g) between left ventricular myocardial oxygen consumption per 100 g muscle mass (MVO_2) and the stress-rate product (HR × S_{peak}) in controls (n = 6) and patients with aortic valve disease and preserved left ventricular function (group 1, n = 19). At a given stress-rate product myocardial oxygen consumption per 100 g muscle mass in group 1 was lower than in the controls (intercept on the MVO_2 axis, 1·0 v 6·1 ml O_2/min × 100 g, $p < 0.001$).



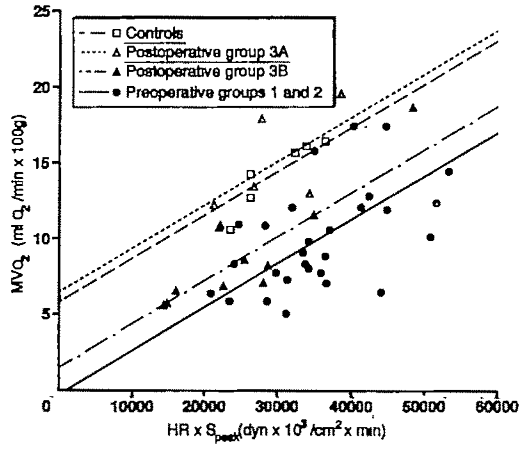
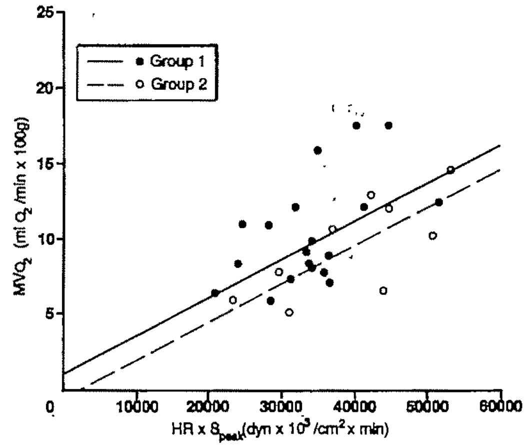


Figure 3 Regression lines (common slope 0·00028 ml O_2 × $cm^2/10^3$ dyn × 100 g) between left ventricular myocardial oxygen consumption per 100 g muscle mass (MVO_2) and the stress-rate product (HR × S_{peak}) in controls (n = 6), in two postoperative patient groups (group 3A, n = 6 and group 3B, n = 10) and in preoperative patients (groups 1 and 2, n = 28). At a given stress-rate product myocardial oxygen consumption per 100 g in preoperative patients was lower than in the controls (intercept: −0·2 v 5·8 ml O_2/min × 100 g, $p < 0.01$). The regression line of myocardial oxygen consumption per 100 g versus the stress rate product in the postoperative group 3B was located between that of the controls (intercept, 1·6 v 5·8 ml O_2/min × 100 g, $p < 0.02$) and that of the preoperative patients (intercept, 1·6 v −0·2 ml O_2/min × 100 g, not significant). In the postoperative group 3A with complete regression of hypertrophy and normal contractility myocardial oxygen consumption per 100 g at a given stress-rate product was higher than in group 3B (intercept, 6·6 v 1·6 ml O_2/min × 100 g, $p < 0.01$) and did not differ from that in the controls.

Figure 2 Regression lines (common slope 0·00025 ml O_2 × $cm^2/10^3$ dyn × 100 g) between left ventricular myocardial oxygen consumption per 100 g muscle mass (MVO_2) and the stress-rate product (HR × S_{peak}) in patients with aortic valve disease and normal (group 1, n = 19) and reduced (group 2, n = 9) ejection fraction. At a given stress-rate product myocardial oxygen consumption per 100 g muscle mass in group 2 patients was lower than in group 1 (intercept, −0·4 v 1·0 ml O_2/min × 100 g, $p < 0.05$).



O_2/min × 100 g) and there were no differences in the determinants of myocardial oxygen consumption—that is, the stress-rate product, left ventricular ejection fraction, and left ventricular muscle mass index (33 671 v 35 643 dyn × $10^3/cm^2$ × min; 65 v 66%, 164 v 156 g/m^2). Similarly, in group 2 these variables were similar in the patients with aortic stenosis (n = 5) and insufficiency (n = 4) (10·1 v 8·8 ml O_2/min × 100 g; 41 412 v 37 217 dyn × $10^3/cm^2$ × min; 46 v 44%; 182 v 155 g/m^2 respectively).

HAEMODYNAMICS AND CORONARY DYNAMICS IN THE POSTOPERATIVE GROUP (TABLES 1 AND 4, FIG 3)

The postoperative patient group included patients who had presented with normal or abnormal left ventricular function before operation. Therefore, the preoperative data available for group 3 were compared with the pooled data of preoperative patients (groups 1 and 2). No differences were found in preoperative aortic valve area (0·8 v 0·7 cm^2) and pressure gradient (69 v 72 mm Hg) in patients with pure or predominant aortic stenosis. Similarly, no difference was found in preoperative regurgitation fraction (51 v 58%) in the patients with pure or predominant aortic insufficiency.

Furthermore, the two patient populations had similar left ventricular ejection fractions, end diastolic volume indices, left ventricular muscle mass indices, left ventricular systolic and end diastolic pressures, heart rates, and cardiac indices. Only the left ventricular end diastolic wall thickness in the pooled pre-

Table 4 Comparison between the pooled preoperative data (mean (SD)) of groups 1 and 2 and the preoperative and postoperative data of group 3

Group	n	EF (%)	EDVI (ml/m²)	h_{ed} (cm)	LMMI (g/m²)	LVSP (mm Hg)	LVEDP (mm Hg)	HR (beats/min)	CI (l/min × m²)
Groups 1 and 2	28	59 (11)	127 (37)	1·15 (0·13)	165 (31)	195 (45)	16 (8)	74 (12)	3·1 (0·5)
Group 3									
Preoperative	16	58 (13)	155 (58)	1·04 (0·16)	159 (39)	173 (41)	18 (10)	69 (12)	3·4 (1·0)
Postoperative	16	67 (7)	92 (12)	0·92 (0·13)	100 (18)	133 (19)	7 (4)	70 (12)	3·5 (0·8‡)
p values:									
1 + 2 v 3 preop*		NS	NS	<0·02	NS	NS	NS	NS	NS
1 + 2 v 3 postop*		<0·01	<0·001	<0·001	<0·001	<0·001	<0·001	NS	NS
3 preop v 3 postop†		<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	NS	NS‡

CI, cardiac index; EDVI, end diastolic volume index; EF, left ventricular biplane ejection fraction; h_{ed}, left ventricular end diastolic wall thickness; HR, heart rate; LMMI, left ventricular muscle mass index; LVEDP, left ventricular end diastolic pressure; LVSP, left ventricular peak systolic pressure.
*Values obtained by unpaired *t* test.
†Values obtained by paired *t* test.
‡n = 13.

operative group was slightly higher than the preoperative wall thickness of group 3 (1·15 v 1·04 cm, $p < 0·02$), reflecting the higher proportion of pressure-overloaded hearts in the pooled preoperative groups 1 and 2 (aortic stenosis 21/28) compared with group 3 (aortic stenosis 10/16).

Postoperatively the group 3 patients showed a considerable improvement in haemodynamic variables compared with their preoperative data and that of the pooled preoperative groups 1 and 2. There was a reduction in the end diastolic volume index, left ventricular systolic pressure and end diastolic pressure, left ventricular end diastolic wall thickness, and muscle mass index. The left ventricular muscle mass index and the interval after successful aortic valve replacement were negatively correlated ($r = -0·50$, $p < 0·05$). The ejection fraction increased in group 3 after operation.

The relation between myocardial oxygen consumption per 100 g and the stress-rate product was compared among controls, patients in groups 3A, 3B, and the pooled preoperative patients of groups 1 and 2 by analysis of covariance (fig 3). Similar regression lines were found for controls and postoperative patients with complete normalisation of left ventricular muscle mass and contractility (group 3A). These two regression lines were above that for the postoperative patients with incomplete postoperative normalisation (group 3B) and that of pooled preoperative patients (groups 1 and 2). Group 3B and preoperative patients (groups 1 and 2) again had similar regression lines.

Multiple regression analysis of the whole study population (50 measurements) showed that the stress-rate product (HR × S_{peak}, $p < 0·0001$), left ventricular muscle mass index (LMMI, $p < 0·002$), and ejection fraction (EF, $p < 0·03$) were significant "explanatory" variables of myocardial oxygen consumption per 100 g (MVo_2/100 g), $r = 0·72$. The following equation was obtained (corresponding standard errors are given in parentheses):

$$MVo_2/100\ g = -0·06 + 0·27\ (0·045)\ HR{\cdot}S_{peak} - 0·04\ (0·01)\ LMMI + 0·11\ (0·048)\ EF$$

where MVo_2/100 g (ml o_2/min × 100 g); HR·S_{peak} (dyn/cm² × min); LMMI (g/m²); EF (%).

The stress-rate product was not correlated with the left ventricular ejection fraction or muscle mass index; but there was a weak negative correlation between left ventricular ejection fraction and muscle mass index ($r = -0·48$). In the stepwise regression the stress-rate product was the first variable entered into the equation ($r^2 = 0·22$), then the left ventricular muscle mass index ($r^2 = 0·47$), and finally r^2 increased to 0·52 when left ventricular ejection fraction was included. When multiple regression analysis was carried out with 32 measurements instead of 50, after patients with aortic valve disease who were older than 58 years (upper limit in the control group) were excluded, the stress-rate product ($p < 0·0001$), left ventricular muscle mass index ($p < 0·0005$), and ejection fraction ($p < 0·04$) remained significant "explanatory" variables of myocardial oxygen consumption per 100 g. Moreover, when age was introduced as an additional variable in the original multiple regression analysis (50 measurements) it was found not to be a significant determinant of myocardial oxygen consumption per 100 g.

Discussion

RELATION BETWEEN MYOCARDIAL OXYGEN CONSUMPTION AND STRESS-RATE PRODUCT

Traditionally, the tension-time index and heart rate are recognised as important determinants of myocardial oxygen consumption.[3 18] Subsequent studies performed in animals[3 19] and in humans[1 2 20] identified left ventricular peak systolic wall stress and the integral of systolic wall stress[21] as major determinants of myocardial blood flow and oxygen consumption. From other studies performed in non-hypertrophied animal hearts it became evident that, contractility, as well as wall stress, has a major influence on the myocardial oxygen consumption.[22 23] Therefore the purpose of the present study was to answer the following questions: first, whether in the chronically overloaded hypertrophied human heart myocardial oxygen consumption per 100 g is related to an analogue of the minute tension-time index—that is, the product of heart rate and peak systolic stress; second, how this relation is modified by chronic alterations in contractility or myocardial hypertrophy or both; and third, what effect regression of hypertrophy has on the relation between myocardial oxygen consumption per 100 g and the stress-rate product.

In patients with aortic valve disease with left ventricular dysfunction and without, in postoperative patients, and in controls we found a significant correlation between the myocardial oxygen consumption per 100 g and the stress-rate product. In addition to this major determinant of myocardial oxygen consumption per 100 g multiple regression analysis showed left ventricular hypertrophy and contractility were further factors that influenced myocardial oxygen consumption per 100 g.

MYOCARDIAL OXYGEN CONSUMPTION IN HYPERTROPHIED AND NON-HYPERTROPHIED VENTRICLES

Our results indicate that myocardial oxygen consumption per 100 g is reduced in left ventricular hypertrophy. Multiple regression showed that the stress-rate product was positively and muscle mass index was negatively correlated with myocardial oxygen consumption per 100 g. This result was confirmed when analysis of covariance (fig 1) showed that the regression line of the stress-rate product and myocardial oxygen consumption per 100 g in group 1 was located below that of the controls. This finding has several possible explanations. First, reduced myocardial oxygen consumption per 100 g at a given level of overall left ventricular performance, represented by the stress-rate product, might be an intrinsic property of the hypertrophied cardiac muscle. Various investigations of human and animal hypertrophied myocardium[24-27] showed that enzymatic and ultrastructural changes develop as a consequence of hypertrophy and result in a slowing of cardiac contraction[28] and improved efficiency at the cellular level. A second explanation may relate to the definition of contractile state in the patients of group 1. In concentric hypertrophy such as in aortic stenosis it is well known that the ejection fraction overestimates left ventricular fibre shortening because thickening of the hypertrophied wall in itself reduces the systolic cavity.[29] Hence a normal ejection fraction does not exclude a slight reduction in contractility[30] which in turn might have caused the decreased myocardial oxygen consumption per 100 g. Finally, does the reduced myocardial oxygen consumption calculated per 100 gram of muscle mass really indicate a reduced oxygen consumption of the myocyte tissue? There is more interstitial tissue per 100 gram of left ventricular muscle mass in hypertrophied than in normal myocardium[31] and interstitial tissue consumes less oxygen than myocyte tissue.

A lower myocardial oxygen consumption per 100 g at a given index of overall left ventricular performance represented by the stress-rate product suggests that the mechanical efficiency per volume unit of the hypertrophied non-failing left ventricular myocardium is greater than that of the normal myocardium. Both Malik *et al*[32] and Su-Fan *et al*[4] reported that the mechanical efficiency of hypertrophied compensated canine left ventricles was greater than that of non-hypertrophied ventricles.

MYOCARDIAL OXYGEN CONSUMPTION IN DIFFERENT CONTRACTILE STATES

Johnson *et al* reported a close relation between coronary blood flow per beat and peak systolic stress ($r = 0{\cdot}97$) in patients with aortic valve disease.[1] However, no direct measurement of left ventricular contractility was performed in that study. Weiss *et al* investigated patients with hypertrophic and congestive cardiomyopathies and found that heart rate, mean velocity of circumferential fibre shortening, and peak systolic stress were the main factors influencing myocardial oxygen consumption; the influence of hypertrophy was not evaluated.[20] Henry *et al* examined 14 patients with valve lesions, cardiomyopathies, and congenital heart diseases and emphasised the importance of the contractile state as a determinant of myocardial oxygen consumption.[33] They did not standardise contractility per unit stress, however, thus neglecting stress as an additional determinant of the myocardial oxygen consumption. In accordance with these findings our study showed that the stress-rate product and muscle mass index were determinants of myocardial oxygen consumption and that the left ventricular ejection fraction was a third determinant of myocardial oxygen consumption/100 g (fig 2).

These results seem to be at variance with the findings of Strauer.[34] He described a low myocardial oxygen consumption in low stress ventricles with preserved ejection fraction and adequate hypertrophy; in contrast, in high stress ventricles with excessive hypertrophy he found a high myocardial oxygen consumption accompanied by a reduced ejection fraction. In that study slight changes in contractility were associated with considerable changes in afterload. In the absence of changes in contractility peak systolic stress becomes the main determinant of myocardial oxygen consumption. In our group 2 patients the decrease in ejection fraction was not the effect of excessive overloading (as in Strauer's study) because peak systolic stress was not different in controls, group 1, and group 2. Thus differences in contractility must have been present. In the group 2 patients mechanical efficiency was likely to be higher and cardiac index was lower than in the controls, which shows that hypertrophied ventricles in which contractility is depressed are unable to transfer the generated energy to the circulation despite an improved efficiency. This paradox was recently discussed by Su-Fan *et al*.[4] They reported that after induction of hypertrophy in canine left ventricles by a combined aortic valve lesion the hypertrophied hearts showed better oxygen utilisation than the controls, but the pressure work increased without a concomitant increase in cardiac output.

MYOCARDIAL OXYGEN CONSUMPTION IN THE POSTOPERATIVE STATE

In the postoperative patients there was a considerable improvement in left ventricular haemodynamic function at rest, and regression, albeit not complete, of myocardial hypertrophy. But what about the postoperative interrelations of myocardial oxygen consumption with peak systolic stress, heart rate, contractility, and muscle mass? Kawachi *et al* reported that in patients with aortic incompetence after operation the peak systolic stress decreased, heart rate remained unchanged, and the ejection fraction increased.[35] The postoperative increase of both the coronary sinus blood flow per beat per 100 g muscle mass and the myocardial oxygen consumption per beat per 100 g was attributed to the postoperative improvement in contractility. To evaluate the influence of postoperative changes in hypertrophy and contractility on myocardial oxygen consumption its relation to the stress-rate product was examined in controls, patients of groups 3A and 3B, and the pooled preoperative patients of groups 1 and 2. As fig 3 shows the regression line of group 3B was located between that of the controls and the preoperative patients, but was not significantly different from that of the preoperative group. The regression line of group 3A was not different from that of the controls. Thus the postoperative patients with full recovery of contractility and complete regression of left ventricular hypertrophy showed that the changes in myocardial oxygen consumption per 100 g and myocardial efficiency were completely reversible.

LIMITATIONS OF THE STUDY

In this study the preoperative patients were divided into two groups based on the assessment of contractility, irrespective of the type of the haemodynamic burden that caused the left ventricular hypertrophy. Differences in several adaptational mechanisms between pressure and volume overload have been reported.[29] However, aortic insufficiency cannot be considered as pure volume load and the degree of left ventricular hypertrophy is known to correlate with the total power requirements, whatever the type of overload.[4,36] Furthermore, Johnson *et al* reported that the relation between the total load and the myocardial oxygen consumption per 100 g was the same when either aortic stenosis or insufficiency was present.[1] We too did not find any difference in myocardial oxygen consumption per 100 g or its determinants (that is, the stress-rate product, left ventricular ejection fraction, and muscle mass index) in patients with aortic stenosis and patients with aortic insufficiency (groups 1 and 2). This is why we do not think that our results were biased by the mixture of aortic valve lesions in each group.

Thermodilution techniques were used to measure total coronary sinus blood flow. Although this method does not measure perfusion in specific transmural layers or different ventricular regions or rapid changes in coronary blood flow,[37] Ganz *et al* found a good correlation between coronary sinus flow measured by this technique and by the timed collection of coronary venous blood.[14] Moreover, transmural distribution of blood flow at rest is likely to be homogeneous in both normal and hypertrophied ventricles whatever the type of overload.[5,38]

In all patient groups the relation between the stress-rate product and the myocardial oxygen consumption per 100 g was significant, though the correlation particularly in groups 1, 2, and 3 was not as close as in studies of paced canine ventricles.[19,21] These differences can be explained at least in part by the following mechanisms: first, by the non-simultaneous measurement of haemodynamic function and the myocardial oxygen consumption in some patients; second, by the different degree of interstitial fibrosis,[31] which we did not take into account; and third, by the likelihood that within the two groups with preserved and reduced contractility there was still considerable heterogeneity of contractility. Moreover we recognise the limitations of peak systolic stress as an index of the mean generated stress during ventricular systole, which would have been a measure more closely reflecting the classic tension-time index.

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1 Johnson LL, Sciacca RR, Ellis K, Weiss MB, Cannon PJ. Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. *Circulation* 1978;57:582–90.

2 Trenouth RS, Phelps NC, Neil WA. Determinants of left ventricular hypertrophy and oxygen supply in chronic aortic valve disease. *Circulation* 1976;53:644–50.

3 Braunwald E. Control of myocardial oxygen consumption. *Am J Cardiol* 1971;27:416–32.

4 Su-Fan Q, Brum JM, Bove AA. Energy production, O_2 consumption, and blood flow reserve in experimental aortic valve disease. *Am J Physiol* 1987;252:243–51.

5 Gaasch WH, Zile MR, Hoshino PK, Apstein CS, Blaustein AS. Stress-shortening relations and myocardial blood flow in compensated and failing canine hearts with pressure-overload hypertrophy. *Circulation* 1989;79:872–83.

6 Thomas DP, Phillips SJ, Bove AA. Myocardial morphology and blood flow distribution in chronic volume-overload hypertrophy in dogs. *Basic Res Cardiol* 1984;79:379–88.

7 Bortone AS, Hess OM, Eberli FR, Nonogi H, Marolf AP, Grimm J, *et al*. Abnormal coronary vasomotion during exercise in patients with normal coronary arteries and reduced coronary flow reserve. *Circulation* 1988;79: 516–27.

8 Eichhorn P, Grimm J, Koch R, Hess O, Carroll J, Krayenbuehl HP. Left ventricular relaxation in patients with left ventricular hypertrophy secondary to aortic valve disease. *Circulation* 1982;65:1395–404.

9 Huber D, Grimm J, Koch R, Krayenbuehl HP. Determinants of ejection performance in aortic stenosis. *Circulation* 1981;64:126–34.

10 Dodge HT, Sandler H, Ballew DW, Lord JD. The use of biplane angiocardiography for the measurement of left ventricular volume in man. *Am Heart J* 1960;60:762–76.

11 Rackley CE, Dodge HT, Coble YD, Hay RE. A method for determining left ventricular mass in man. *Circulation* 1964;29:666–71.

12 Sandler H, Dodge HT. Left ventricular tension and stress in man. *Circ Res* 1963;13:91–104.

13 Gaasch WH, Battle WE, Oboler AA, Banas JS, Levine HJ. Left ventricular stress and compliance in man with special reference to normalized ventricular function curves. *Circulation* 1972;45:746–62.

14 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971;44:181–95.

15 Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. *Circulation* 1978;57:778–86.

16 Foult JM, Nitenberg A. Dipyridamole versus intracoronary injection of contrast medium for the evaluation of coronary reserve in man: a comparative study. *Cathet Cardiovasc Diagn* 1986;12:304–10.

17 Neter J, Wasserman W, Kutner JH. *Applied linear statistical models*. 2nd ed. Homewood, Illinois: Irwin, 1985:856–73.

18 Sarnoff SJ, Braunwald E, Welch GH, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen

consumption of the heart with special reference to the tension-time index. *Am J Physiol* 1958;**192**:148–56.

19 McDonald RH Jr, Taylor RR, Cingolani HE. Measurement of myocardial developed tension and its relation to oxygen consumption. *Am J Physiol* 1966;**211**:667–73.

20 Weiss MB, Ellis K, Sciacca RR, Johnson LL, Schmidt DH, Cannon PJ. Myocardial blood flow in congestive and hypertrophic cardiomyopathy. *Circulation* 1976;**54**: 484–94.

21 Weber KT, Janicki JS, Myocardial oxygen consumption: the role of wall force and shortening. *Am J Physiol* 1977;**233**:421–30.

22 Graham TP Jr, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. *J Clin Invest* 1968;**47**:375–85.

23 Downey JM. Myocardial contractile force as a function of coronary blood flow. *Am J Physiol* 1976;**230**:1–6.

24 Kozlovskis PL, Fieber LA, Pruitt DK, Bailey BK, Smets MJD, Bassett Al, *et al.* Myocardial changes during the progression of left ventricular pressure-overload by renal hypertension or aortic constriction: myosin, myosin ATPase and collagen. *J Mol Cell Cardiol* 1987;**19**: 105–14.

25 Kjeldsen K, Bjerregaard P, Richter EA, Block Thomsen PE, Norgaard A. Na^+/K^+-ATPase concentration in rodent and human heart and skeletal muscle: apparent relation to muscle performance. *Cardiovasc Res* 1988;**22**:95–100.

26 Peters TJ, Wells G, Oakley CM, Brooksby IAB, Jenkins BS, Webb-Peploe MM, *et al.* Enzymic analysis of endomyocardial biopsy specimens from patients with cardiomyopathies. *Br Heart J* 1977;**39**:1333–9.

27 Ferrans VJ. Human cardiac hypertrophy: structural aspects. *Eur Heart J* 1982;**3**(suppl A):15–27.

28 Swynghedauw B. Remodelling of the heart in response to chronic mechanical overload. *Eur Heart J* 1989;**10**: 935–43.

29 Krayenbuehl HP, Hess O, Hirzel H. Pathophysiology of the hypertrophied heart in man. *Eur Heart J* 1982;**3(suppl A)**:125–31.

30 Krayenbuehl HP, Hess OM, Ritter M, Monrad ES, Hoppeler H. Left ventricular systolic function in aortic stenosis. *Eur Heart J* 1988;**9(suppl E)**:19–23.

31 Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve repalcement. *Circulation* 1989;**79**:744–55.

32 Malik AB, Abe T, O'Kane H, Geha AS. Cardiac function, coronary flow, and oxygen consumption in stable left ventricular hypertrophy. *Am J Physiol* 1973;**225**:186–91.

33 Henry PD, Eckberg D, Gault JH, Ross J Jr. Depressed inotropic state and reduced myocardial oxygen consumption in the human heart. *Am J Cardiol* 1973;**31**:300–6.

34 Strauer BE. Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. *Am J Cardiol* 1979;**44**:730–40.

35 Kawachi K, Kawashima Y, Kitamura S, Mori T, Hirose H, Nakano S, *et al.* Coronary sinus blood flow and myocardial oxygen consumption after valve replacement for aortic insufficiency. *Ann Thorac Surg* 1986;**42**:86–9.

36 Baxley WA, Dodge HT, Rackley CE, Sandler H, Pugh D. Left ventricular mechanical efficiency in man with heart disease. *Circulation* 1977;**55**:564–8.

37 Marcus ML, Wilson RF, White CW. Methods of measurement of myocardial blood flow in patients: a critical review. *Circulation* 1987;**76**:245–53.

38 Breisch EA, Houser SR, Carey RA, Spann JF, Bove AA. Myocardial blood flow and capillary density in chronic pressure overload of feline left ventricle. *Cardiovasc Res* 1980;**14**:469–75.

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Use of transoesophageal echocardiography to detect left atrial thrombi before percutaneous balloon dilatation of the mitral valve: a prospective study

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Abstract

Objective—Systemic emboli related to atrial thrombi are a well known complication of percutaneous balloon dilatation of the mitral valve. The presence of left atrial thrombi therefore, is believed to be a contraindication to balloon dilatation. The purpose of this study was to determine the frequency of left atrial thrombi in patients referred for balloon dilatation of the mitral valve, the added benefit of pre-procedural transoesophageal echocardiography, and to identify factors that predicted left atrial thrombi.

Design—Prospective study over a 14 month period of 20 consecutive patients by cross sectional transthoracic echocardiography 24–48 hours before balloon dilatation of the mitral valve and by transoesophageal echocardiography immediately before the procedure.

Results—One patient had a left atrial thrombus detected by transthoracic study. Two patients (10%) had left atrial thrombi identified by transoesophageal echocardiography. In both valve dilatation was not attempted and the thrombi were confirmed at surgery. The remaining 18 patients all underwent successful balloon dilatation of the mitral valve without clinical evidence of an embolic event. No association was found between patient age, mitral valve area, transmitral gradient, left atrial size, presence of atrial fibrillation, severity of mitral regurgitation, cardiac output, or the presence of left atrial swirling and an increased prevalence of atrial thrombi.

Conclusion—Left atrial thrombi are often seen despite long term systemic anticoagulation in patients referred for balloon dilatation of the mitral valve. The frequency of unsuspected left atrial thrombi detected by transoesophageal echocardiography was similar to the reported frequency of embolic events after balloon dilatation of the mitral valve. Transoesophageal echocardiography for the identification of left atrial thrombi is strongly recommended in all patients before balloon dilatation of the mitral valve including those treated with systemic anticoagulation and those who have had a normal transthoracic echocardiographic study.

The technique of percutaneous balloon dilatation of the mitral valve by the transseptal approach has been generally accepted as an alternative to mitral valve replacement or surgical commissurotomy in a subgroup of patients with symptomatic mitral stenosis.[1 2] Mitral stenosis is frequently associated with left atrial thrombi[3] and systemic emboli are a well known complication of balloon dilatation of the mitral valve (incidence 4%).[4] These events are believed to be caused primarily by embolisation of left atrial thrombi, when a thrombus is dislodged during the procedure. So the presence of left atrial thrombi is thought to be a contraindication to balloon dilatation of the mitral valve. Recently, transoesophageal echocardiography has been shown to be much better than conventional cross sectional transthoracic echocardiography for the identification of left atrial thrombi.[5-7] The purpose of this study was to evaluate the role of routine transoesophageal echocardiography for the identification of left atrial thrombi before the procedure.

Patients and methods

PATIENTS

We studied 20 consecutive patients (18 women and two men aged 41–79 years (mean 59 years)) referred for elective balloon dilatation of the mitral valve from 1 December 1989 to 28 February 1991. Three patients had undergone earlier surgical commissurotomies and nine patients were in chronic atrial fibrillation. All 20 patients had been treated with sodium warfarin (therapeutic prothrombin times >1·5 times control) for at least eight weeks before planned balloon dilatation of the mitral valve. No patient had a history of an earlier embolic event. Coumadin was stopped two days before admission. The identification of an atrial thrombus was thought to be an indication for mitral valve replacement. Patients undergoing balloon dilatation of the mitral valve were followed clinically throughout their stay in hospital for evidence of systemic emboli.

Written informed consent was obtained from all patients.

TRANSTHORACIC ECHOCARDIOGRAPHY

Patients underwent conventional transthoracic cross sectional and Doppler echocardiographic examination 12–36 hours before the planned balloon dilatation of the mitral valve by techniques reported previously.[8] Cross sectional imaging studies were performed in the parasternal long axis, parasternal short axis, apical, and subcostal views by a Sonos 500 or Sonos 1000 (Hewlett-Packard) echocardiograph and both 2·5 MHz and 5·0 MHz phased array transducers. The left atrial anteroposterior diameter was measured in the parasternal long axis view according to the American Society of Echocardiography criteria.[9] Left atrial length was assessed in the four chamber apical view. Mitral valve area was assessed by the pressure half time technique.[8] Spontaneous contrast was defined as the presence of dynamic echoes (smoke-like) in a circular pattern within the left atrium.[10]

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

All patients underwent transoesophageal echocardiography examination after an overnight fast and within two hours of the scheduled balloon dilatation of the mitral valve (n = 18) or the day before the planned procedure (n = 2). Local anaesthesia to the posterior pharynx was accomplished with 10% lignocaine spray. Antibiotics for endocarditis prophylaxis were given to all patients according to the recommendations of the American Heart Association.[11] Transoesophageal echocardiography was performed with a commercial single plane 5·0 MHz transoesophageal echocardiography probe (Hewlett-Packard). Images of the cardiac chambers, valves, and great vessels were recorded on videotape for review. Special attention was paid to the left atrium and the left atrial appendage.

BALLOON DILATATION OF THE MITRAL VALVE

Patients in whom there was no evidence of atrial thrombi by transthoracic or transoesophageal echocardiography underwent balloon dilatation of the mitral valve with a single 25 mm Mansfield balloon (Mansfield Scientific, Waltham, Massachusetts) by the transseptal approach.[2] Fick cardiac output was obtained in all patients before placement of the transseptal needle.[12]

Six additional patients with rheumatic mitral stenosis underwent transoesophageal echocardiographic study to identify left atrial thrombi while under general anaesthesia in the operating room before mitral valve replacement. These patients were not candidates for balloon dilatation of the mitral valve because there was concomitant aortic stenosis (n = 2) or important mitral regurgitation (n = 4).

DATA ANALYSIS

All data are expressed as mean (SD). The statistical significance of left atrial size, Doppler variables, and catheterisation cardiac output/index was assessed by Student's unpaired *t* test. Fischer's exact test was used to compare dichotomous variables. A p value of <0·05 was considered statistically significant.

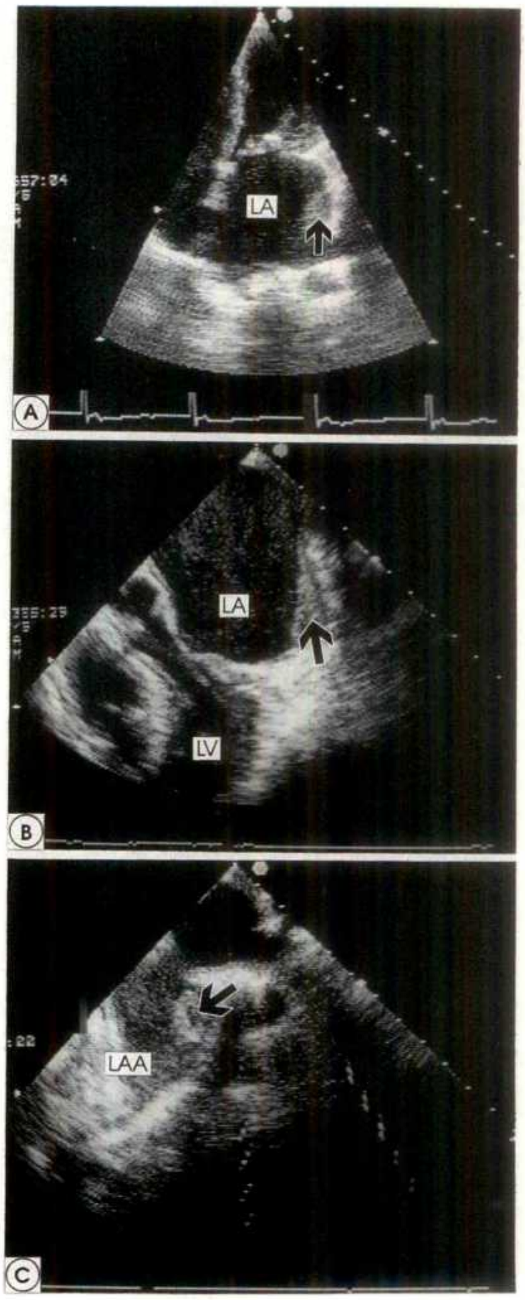

Figure 1 (A) Transthoracic apical four-chamber view of the heart obtained with a 5 MHz imaging transducer. Note the thrombus (arrow) along the lateral wall of the left atrium (LA). (B) Transoesophageal echocardiography. Note the thrombus (arrow) lining the lateral wall of the left atrium and spontaneous contrast within the left atrium. LV, left ventricle. (C) Transoesophageal echocardiography study of the left atrial appendage (LAA) of the same patient shown in A and B. Note the second thrombus (arrow).

Results

Transthoracic echocardiographic study identified a probable thrombus in one patient scheduled for balloon dilatation. The thrombus was located along the lateral wall of the left atrium (fig 1A).

All patients tolerated transoesophageal echocardiography without complications. Imaging of the left atrial appendage was

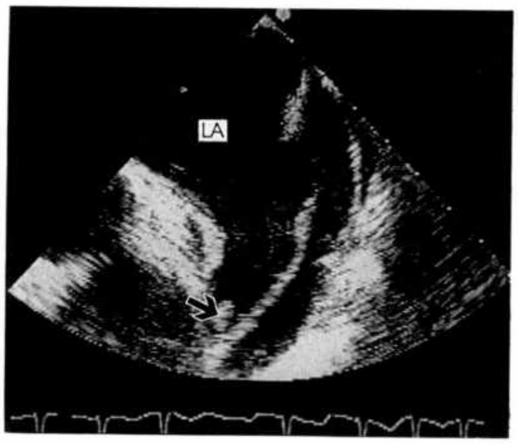

Figure 2 Transoesophageal echocardiography view of the left atrium in another patient. Note the thrombus (arrow) in the distal portion of the left atrial appendage.

successful in all 18 patients in whom it was present. In two patients the left atrium had been either oversewn (n = 1) or amputated (n = 1) during an earlier surgical commissurotomy. Transoesophageal echocardiography confirmed the thrombus seen by transthoracic study (fig 1B) and also identified a second thrombus in this patient, which was confined to the left atrial appendage (fig 1C). Transoesophageal echocardiography also identified a thrombus confined to the distal left atrial appendage in another patient (fig 2). We found left atrial thrombi in 10% of patients referred for balloon dilatation of the mitral valve. In both instances in which a thrombus was identified patients were referred for mitral valve replacement and the site and presence of all thrombi were confirmed at the time of surgery. The remaining 18 patients underwent balloon dilatation of the mitral valve without evidence of an embolic event during their hospital stay.

The table shows the characteristics of the subgroups with and without atrial thrombi. Patient age, atrial fibrillation, mitral valve area, mitral valve gradient, cardiac output/index, severity of mitral regurgitation, and presence of left atrial swirling were not predictive of thrombi (table). Total echo score[13] was also not predictive.

No thrombi were identified by transoesophageal echocardiographic study in any of the patients with rheumatic mitral stenosis scheduled for mitral valve replacement. The table shows the characteristics of this group of patients. Visual inspection of the left atrium also failed to reveal any thrombi.

Comparison of echocardiographic and catheterisation data in patients with left atrial thrombi and without

Variable	*With LA thrombus (n = 2)*	*No LA thrombus (dilatation) (n = 18)*	*No LA thrombus (replacement) (n = 6)*
Age (yr)	52 (41–63)	60 (41–79)	59 (40–67)
Atrial fibrillation	2 (100%)	7 (39%)	4 (67%)
Left atrial dimension (cm)	5·4 (0·5)	5·4 (0·7)	5·9 (0·2)
Four chamber left atrial length (cm)	6·5 (0·2)	6·4 (1·0)	7·7 (1·1)
Mitral valve area (cm^2)	0·7 (0·1)	1·1 (0·4)	1·1 (0·6)
Mitral valve gradient (mm Hg)	8·8 (0·3)	8·5 (3·4)	9·0 (5·0)
Cardiac output (l/min)	4·3 (0·2)	4·5 (1·4)	
Cardiac index (l/min/m^2)	2·7 (0·2)	2·7 (0·7)	
Severity of MR (0–3)	1·3 (0·4)	0·9 (0·5)	2·0 (0·7)*
Left atrial swirling (TTE)	1 (50%)	3 (15%)	1 (17%)
Left atrial swirling (TOE)	1 (50%)	6 (33%)	2 (33%)
Echo score (0–16)	8 (3)	6 (2)	9 (2)*

*$p < 0.05$ *v* no LA thrombus (dilatation). MR, mitral regurgitation; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram.

Discussion

Systemic embolisation is a recognised complication of balloon dilatation of the mitral valve. It occurs in up to 4% of patients.[4] The ability to identify and exclude those patients at high risk of systemic emboli would significantly reduce the morbidity of this procedure. Transthoracic echocardiography has a low sensitivity for detection of left atrial thrombi, particularly those in the left atrial appendage.[7] Transoesophageal echocardiography gives superior visualisation of the appendage, and previous studies showed it was a more sensitive detector of left atrial thrombi.[5 6]

The present study shows that transoesophageal echocardiography can be safely performed and can accurately detect and localise left atrial thrombi in patients with severe mitral stenosis referred for balloon dilatation of the mitral valve. Despite chronic systemic anticoagulation 10% of patients studied had left atrial thrombi which we confirmed at surgery. Our findings are consistent with those of Kronzon *et al* who reported that 26% of patients undergoing transoesophageal echocardiography before balloon dilatation of the mitral valve had a detectable left atrial clot.[14] The lower frequency of thrombi in our study may be related to the use of at least two months of systemic anticoagulation in our patients. Kronzon *et al*, however, did not examine risk factors that were potentially predictive for the development of atrial thrombi. Low cardiac output and age have been reported as risk factors for systemic emboli in patients with mitral stenosis.[3] Our findings suggest that patient age, atrial fibrillation, left atrial size, mitral valve gradient, cardiac output, severity of mitral regurgitation, left atrial swirling, and echo score did not predict the presence of atrial thrombi in our group of anticoagulated patients. There was a trend towards a smaller mitral valve area in the group with atrial thrombi but this did not achieve statistical significance. Thus we were unable to identify any descriptors that might be useful in deciding which patients, if any, are at sufficiently low risk for left atrial thrombi that a transoesophageal echocardiography may be omitted.

Spontaneous left atrial contrast in mitral stenosis has been suggested as an indicator for an increased risk of thromboembolism[15] and atrial thrombosis. Spontaneous contrast is felt to be related to the rouleaux formation of erythrocytes which occur during slow flow conditions.[16] In vitro and in vivo experiments showed that blood within isolated vessels may become echogenic within a few seconds after the onset of stasis induced by cross clamping.[16] In addition, fibrinogen or its products plus red blood cells are needed to create echogenicity of static liquid blood. This phenomenon is not prevented by heparin. We did not find the presence of spontaneous left atrial contrast to be predictive for left atrial thrombi. Our study population, however, was small and all our patients were systemically anticoagulated.

Patients with left atrial thrombi identified by transthoracic study are usually not referred for balloon dilatation of the mitral valve. The additional 5% frequency of left atrial thrombi identified by transoesophageal echocardiography in our study is similar to the reported incidence of embolic events with balloon dilatation reported in large series.[4] Most patients in these large series have *not* undergone pre-procedural transoesophageal echocardiography. While the exact frequency of embolisation in patients with atrial thrombi is unknown, it is reasonable to assume that they are at higher risk than patients without thrombi.

LIMITATIONS

Although systemic emboli are often related to dislodgement of atrial thrombi, some of these events may be due to thrombi forming on catheters and guide wires, to debris released with commissure fracture,[2] or to balloon rupture.[17] These events would not be avoided by a pre-procedural transoesophageal echocardiography. A decreased incidence of embolic events also cannot be estimated by this study. While no subject in our study had evidence of systemic emboli, a much larger study will be needed to determine whether patients with negative transoesophageal echocardiography examinations have a lower risk of embolisation or if the frequency of embolic events would be reduced if balloon dilatation of the mitral valve were avoided in patients with thrombi identified by transoesophageal echocardiography.

CONCLUSION

Left atrial thrombi are often seen despite long term systemic anticoagulation in patients referred for balloon dilatation of the mitral valve. The frequency of unsuspected left atrial thrombi detected by transoesophageal echocardiography is similar to the incidence of embolic events reported with balloon dilatation.

We strongly recommend transoesophageal echocardiography to identify left atrial thrombi before balloon dilatation of the mitral valve, including patients treated with systemic anticoagulation and those who have had a normal transthoracic study. The identification of a left atrial thrombus should be considered a contraindication to the balloon dilatation of the mitral valve and such patients should be referred for mitral valve replacement or open surgical commissurotomy.

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1 Inoue K, Owaki T, Nakamara T, Kitamura F, Miamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;87:394–402.

2 McKay RG, Lock JE, Safian RD, *et al.* Balloon dilation of mitral stenosis in adult patients: postmortem and percutaneous mitral valvuloplasty studies. *J Am Coll Cardiol* 1987;9:723–31.

3 Braunwald E. Valvular heart disease. In: Braunwald E, ed. *Heart disease.* 3rd ed. Philadelphia: WB Saunders, 1988:1023–34.

4 Kulick DL, Reid CL, Kawanishi DT, Rahimtoola SH. Catheter balloon commissurotomy in adults. Part II: Mitral and other stenoses. *Curr Probl Cardiol* 1990; 15:397–470.

5 Aschenberg W, Schlüter M, Kremer P, Schroder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986;7:163–6.

6 Pearson AC, Labovitz AJ, Tatineni S, Gomez CR. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. *J Am Coll Cardiol* 1991;17:66–72.

7 Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleja HB. Two-dimensional echocardiographic diagnosis of left atrial thrombus in rheumatic heart disease: a clinicopathologic study. *Circulation* 1983;67:341–7.

8 Come PC, Riley MF, Diver DJ, Morgan JP, Safian RD, McKay RG. Noninvasive assessment of mitral stenosis before and after percutaneous balloon mitral valvuloplasty. *Am J Cardiol* 1988;61:817–25.

9 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–83.

10 Castello R, Pearson AC, Labovitz AJ. Prevalence and clinical implications of atrial spontaneous contrast in patients undergoing transoesophageal echocardiography. *Am J Cardiol* 1990;65:1149–53.

11 Shulman ST, Amren DP, Bisno AL, *et al.* Prevention of bacterial endocarditis. *Circulation* 1984;70:1123A–7A.

12 Grossman W. Blood flow measurement: the cardiac output. In: Grossman W, ed. *Cardiac catheterization and angiography*. 3rd ed. Philadelphia: Lea & Febinger, 1986: 101–17.

13 Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;60: 299–308.

14 Kronzon I, Tunick PA, Glassman E, Slater J, Schwinger M, Freedberg RS. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. *J Am Coll Cardiol* 1990;16:1320–22.

15 Daniel WG, Nellessen U, Schröder E, *et al.* Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. *J Am Coll Cardiol* 1988;11:1204–11.

16 Sigel B, Coelho JCU, Spigos DG, *et al.* Ultrasonography of blood during stasis. *Invest Radiol* 1981;16:71–6.

17 Vahanian A, Michel PL, Cormier B, *et al.* Results of percutaneous mitral commissurotomy in 200 patients. *Am J Cardiol* 1989;63:847–52.

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Epicardial damage induced by topical cooling during paediatric cardiac surgery

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Abstract

Objective—**To study electrocardiographic changes in infants and children in whom topical cooling was used during surgical repair of congenital heart defects.**

Design—**A retrospective study of all patients who had surgical repair of congenital heart disease during cold blood cardioplegia and topical cooling from January to August 1990. Eleven patients (group 1) had topical cooling with ice and 15 (group 2) with cold saline.**

Patients—**All 36 paediatric patients operated on during this period. All the available electrocardiographic records were analysed. Ten patients in whom reliable records were not available were excluded. Twenty six patients entered in this retrospective study.**

Interventions—**Topical cooling with ice or with a slush of cold saline.**

Main outcome measure—**Recordings from all the precordial leads were examined and scored as the sum of the maximum ST elevation (mV) in each precordial lead. The score obtained for each electrocardiogram was recorded together with the timing of the electrocardiogram (preoperative, arrival in intensive care unit immediately after surgery, postoperatively in the intensive care unit, and at discharge).**

Results—**There were no differences between the two groups in terms of demographic data, diagnosis, duration of ischaemia, and postoperative myocardial performance. There was temporary ST elevation during the first 48 postoperative hours in all the children in group 1 but in only seven of the 15 children in group 2 (Fisher's test, $p < 0.005$). The mean (SD) score for maximum ST elevation was 1·34 (0·83) mV in group 1 and 0·52 (0·64) mV in group 2 (Student's t test, $p < 0.01$).**

Conclusions—**These temporary electrocardiographic changes in the presence of adequate myocardial performance were attributed to epicardial damage induced by hypothermic-osmotic injury. The use of ice for topical cooling may damage the epicardium in children.**

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Topical cardiac hypothermia, used alone or in conjunction with cold cardioplegia, is a simple and effective means of protecting the myocardium during cardiac surgery.[1-15] Topical cooling, however, can damage the phrenic nerve[1 2 4 8-11] and the myocardium.[16-23] We saw temporary electrocardiographic variations that were probably caused by epicardial damage in children in whom topical cooling was used during surgical repair for congenital heart defects.

Patients and methods

From January to August 1990 36 children had surgical repair of a congenital heart defect on cardiopulmonary bypass. In all patients the myocardium was protected by moderate hypothermia, cold blood cardioplegia, modified warm blood reperfusion, and topical cooling during the ischaemic period.

Initially (January to April 1990) we used ice for topical cooling. Later (April to August 1990) we used a slush of cold saline (4–8°C) without ice. We retrospectively compared the patients treated by these two methods in terms of age, weight, diagnosis, duration of cardiopulmonary bypass and aortic cross clamping time, myocardial enzymes (creatine kinase and creatine kinase MB), electrocardiograms, and clinical indices in the intensive care unit (peripheral pulses, peripheral temperature, oxygen saturation of the mixed venous blood, time of extubation, need for inotropic support, length of stay).

All the available electrocardiograms were analysed. We examined the traces from all the precordial leads and obtained an arbitrary score by adding the maximum ST elevation (mV) seen in each precordial lead.[24 25] The score for each electrocardiogram was recorded, together with the timing of the electrocardiogram (that is, preoperative, arrival in the intensive care unit immediately after surgery, postoperatively in the intensive care unit, and at discharge).

We excluded patients for whom we did not have a complete set of electrocardiograms and those who required activation of an external pacemaker during the postoperative electrocardiographic recording. All the electrocardiograms were analysed by a cardiologist (CC) who was unaware of the type of topical cooling used and of the timing of the electrocardiogram.

We used Fisher's test to compare the two groups in terms of the presence or absence of ST elevation and Student's t test to compare the two groups in terms of the score for maximum ST elevation. A probability of <0.05 was regarded as significant.

Table 1 Clinical data

Data	*Group 1* *(topical cooling with ice)*	*Group 2* *(topical cooling without ice)*
Number of patients	11	15
Mean age (range) (yr)	7·7 (4·4–15·1)	5·8 (0·8–14·2)
Mean weight (range) (kg)	25·0 (15–56)	19·3 (6–47)
Mean duration of CPBP (range) (min)	53 (36–70)	72 (28–150)
Mean aortic cross clamp (range) (min)	22 (12–37)	35 (7–74)
Mean CK (range) (U/l)	674 (147–2130)	874 (318–1642)
Mean CK MB (range) (U/l)	61 (20–118)	98 (37–196)

CPBP, cardiopulmonary bypass; CK, creatine kinase.
There were no significant differences between group 1 and group 2 (Wilcoxon test).

Results

We analysed data for 11 patients who had topical cooling with ice (group 1) and 15 patients who had topical cooling without ice (group 2) (table 1). The diagnoses in group 1 patients were subaortic stenosis four, atrial septal defect three, aortic valve stenosis two, partial atrioventricular septal defect one, and partial anomalous pulmonary venous connection one. In group 2 patients the diagnoses were atrial septal defect five, ventricular septal defect three, partial atrioventricular septal defect two, tetralogy of Fallot two, subaortic stenosis one, aortic valve stenosis one, and partial anomalous pulmonary venous connection one.

There were no significant differences between the two groups in terms of age, weight, duration of cardiopulmonary bypass, duration of aortic cross clamping, and activity of creatine kinase and creatine kinase MB (table 1). Nor were there any differences between the two groups in terms of the indirect signs of adequate cardiac output during the postoperative course (peripheral pulses, peripheral temperature, oxygen saturation of the mixed venous blood), early extubation, the need for inotropic support, and stay in the intensive care unit.

All patients in group 1 showed ST elevation in the first 48 hours after operation but only seven (47%) of the patients in group 2 ($p < 0·005$). In group 1 the mean (SD) of the highest electrocardiographic scores was 1·34 (0·83) (0·5–2·85) mV whereas in group 2 it was 0·52 (0·64) (0–1·5) mV, ($p < 0·01$) (table 2). None of the patients had electrocardiographic changes on the first postoperative recording (at arrival in the intensive care unit). The ST changes became evident 8–16 hours after operation and then progressively diminished 24–48 hours after operation. No ST segment elevation was seen on any of the electrocardiograms recorded at discharge (figure).

Table 2 Electrocardiographic scores (mV)

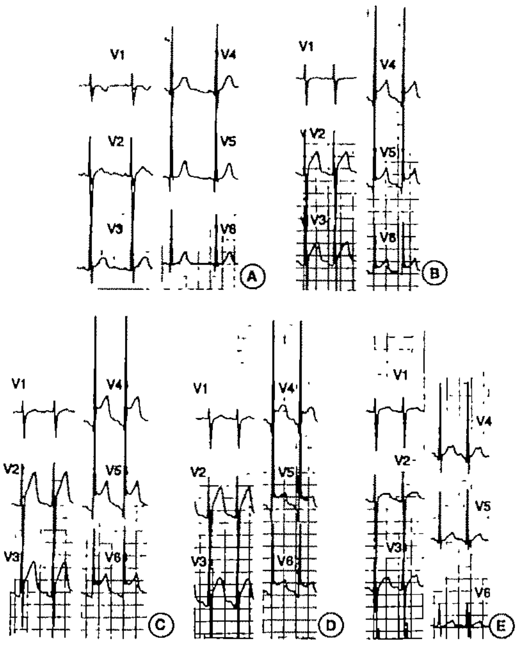
Patient	*ECG score (mV)*
Group 1 *(topical cooling with ice)*	
1	1·50
2	1·90
3	0·75
4	1·40
5	1·40
6	0·50
7	0·15
8	2·30
9	2·85
10	0·40
11	1·55
Mean (SD)	1·34 (0·83)
Group 2 *(topical cooling without ice)*	
1	0·25
2	1·50
3	1·30
4	1·45
5	0
6	1·20
7	0
8	0·95
9	0
10	1·20
11	0
12	0
13	0
14	0
15	0
Mean (SD)	0·52 (0·64)

Discussion

Topical cooling has been reported to provide better structural and functional protection of the myocardium in children than in adults.[26-28] The myocardial protection provided by topical cooling is even more efficient in neonates than in children. Faster and more uniform cooling can be obtained in the neonatal heart because it has a relatively small cardiac mass and a greater surface/wall thickness ratio than the adult heart.[27] In an experimental study of the isolated, blood perfused neonatal heart adequate myocardial recovery was reported after two hours of ischaemia with topical cooling as the only method of myocardial protection.[27] We have always used topical cooling with blood cardioplegia for myocardial protection in our paediatric patients. Damage to the phrenic nerve[1 2 4 8-11] and to the myocardium[16-23] induced by topical cooling has often been reported but we were unaware of epicardial damage in children with this method of myocardial protection.

In our retrospective study we found evidence of temporary ST changes in all the patients in whom topical cooling was achieved with ice (group 1) but in only half of those in whom topical cooling was achieved with cold saline without ice (group 2). Whatever the method we used for topical cooling myocardial protection was adequate in all our patients. We therefore examined the possibility that the epicardium had been temporarily damaged by prolonged direct contact with the ice. An interesting study showed that ice crystals only form after the saline is "supercooled" to −7°C and that this causes the surrounding cold solution to become hyperosmotic.[18] This thermodynamic effect could lead to hypothermic-osmotic tissue damage during topical cardiac cooling. The commonest example of this is paralysis of the phrenic nerve.[1 2 4 8-11]

The degree of hypothermic-osmotic damage that could be caused by topical cooling of the myocardium is less well understood. Direct hypothermic damage to the heart muscle may result in disorganisation of the protoplasmic structure of the cell surface, possibly by drastically dehydrating the fluid layer surrounding the protoplasmic surface.[18] Muscle cell membranes start to leak and proteins become denatured when their temperature is lowered to a critical "point of no return". This "point of no return", however,



Electrocardiogram in a child (case 9) in whom ice was used for topical cooling (group 1). (A) preoperative recording; (B), (C), and (D) 6, 11, and 16 hours postoperatively; (E) at discharge.

has never been accurately defined.[18] Electron microscopic studies of smooth muscle preparations showed that this process was already evident at temperatures as high as −2·5°C.[23]

As the muscle is frozen to −20°C more and more cells show signs of severe structural damage such as disrupted plasma membranes and mitochondria, gross alterations to contractile myofilaments, complete disintegration of myofilaments and shrinkage of nuclei.[23] Walter also found that hypertonic salt solutions damaged smooth muscle and he concluded that sodium chloride is the electrolyte that is most likely to cause damage during freezing and thawing.[23] Furthermore the myocardial storage temperature affects the recovery of calcium ATPase: after storage at 0–4°C recovery of calcium ATPase function was poor, which may be an explanation for the abnormal relaxation of stored myocardium.[16]

We examined our clinical experience in the light of these reported experimental observations. We found that (*a*) the electrocardiographic changes we saw were completely different from the T wave changes seen after the pericardiotomy; (*b*) the electrocardiographic changes occurred even when myocardial performance was adequate. (This fact supports our hypothesis that the temporary ST elevation was an expression of epicardial damage without depression of the myocardial function.); (*c*) the ST changes coincided with the appearance of epicardial oedema within a few hours of the hypothermic-osmotic damage, and subsequently disappeared with routine fluid restriction and use of diuretics in the first 48 hours after operation.

We conclude that (*a*) the topical cooling obtained with ice may induce temporary epicardial damage in children even when there are no adverse clinical occurrences; (*b*) the potential for hypothermic-osmotic injury should be borne in mind whenever topical cardiac hypothermia is used; (*c*) epicardial damage can be avoided if cold saline is used instead of ice for topical cooling (cold blood cardioplegia with modified reperfusion and topical cooling with cold saline gives adequate myocardial protection).

1 Brody WR, Reitz BA. Topical hypothermia protection of the myocardium. *Ann Thorac Surg* 1975;20:66.

2 Cohn LH, Collins JJ. Local cardiac hypothermia for myocardial protection. *Ann Thorac Surg* 1974;17:135.

3 Cross RS, Jones RD, Berne RM. Localised cardiac hypothermia as an adjunct to elective cardiac arrest. *Surg Forum* 1957;8:355–63.

4 Griepp RB, Stinson EB, Oyer PE, Copeland JG, Shumway NE. The superiority of aortic cross-clamping with profound local hypothermia for myocardial protection during aorta-coronary bypass grafting. *J Thorac Cardiovasc Surg* 1975;70:995–1009.

5 Holland CE, Olson RE. Prevention by hypothermia of paradoxical calcium necrosis in cardiac muscle. *J Mol Cell Cardiol* 1975;7:917–28.

6 Hufnagel CA, Conrad PW, Schanno J, Pifarré R. Profound cardiac hypothermia. *Ann Surg* 1961;153:790–6.

7 Koster JK, Cohn LH, Collins JJ, Sanders JH, Muller JE, Young E. Continuous hypothermic arrest versus intermittent ischemia for myocardial protection during coronary revascularisation. *Ann Thorac Surg* 1977;24:330.

8 Lazar HL, Rivers S. Importance of topical hypothermia during heterogeneous distribution of cardioplegic solution. *J Thorac Cardiovasc Surg* 1989;98:251–7.

9 Laschinger JC, Catinella FP, Cunningham JN, Knopp EA, Nathan IM, Spencer FC. Myocardial cooling: beneficial effect of topical hypothermia. *J Thorac Cardiovasc Surg* 1982;84:807–14.

10 Pupello DF, Blank LH, Bessone LN, Connar RG, Carlton LM. Local deep hypothermia for combined valvular and coronary heart disease. *Ann Thorac Surg* 1976;21:508.

11 Sanger PW, Robicsek F, Daugherty HK, Gallucci V, Lesage MA. Topical cardiac hypothermia in lieu of coronary perfusion. *J Thorac Cardiovasc Surg* 1966;52:533–41.

12 Schraut W, Lamberti JJ, Kampman K, Anagnostopoulos C, Replogle R, Glagov S. Does local cardiac hypothermia during cardiopulmonary bypass protect the myocardium from long-term morphological and functional injury? *Ann Thorac Surg* 1977;24:315.

13 Shragge BW, Digerness SB, Blackstone EH. Complete recovery of myocardial function following cold exposure. *Circulation* 1978;58 (suppl II):II–97.

14 Shumway NE, Lower RR, Stofer RC. Selective hypothermia of the heart in cardiac arrest. *Surg Gynecol Obstet* 1959;100:750–4.

15 Swanson DK, Dufek JH, Kahn DR. Improved myocardial preservation at 4°C. *Ann Thorac Surg* 1980;30:519–26.

16 Labow RS, Meek E, Hendry PJ, Keon WJ. Temperature affects human sarcoplasmatic reticulum calcium ATPase. *J Mol Cell Cardiol* 1990;22 (suppl V):12.

17 Rittenhouse EA, Mohri H, Reichenbach DD, Merendino KA. Morphological alterations in vital organs after prolonged cardiac arrest at low body temperature. *Ann Thorac Surg* 1972;13:564–74.

18 Robicsek F, Duncan GD, Rice HE, Robicsek SA. Experiments with a bowl of saline: the hidden risk of hypothermic-osmotic damage during topical cardiac cooling. *J Thorac Cardiovasc Surg* 1989;97:461–6.

19 Rosenfeldt FL, Cochrane AD. When is hypothermic technique inadequate? How can it be improved? *J Mol Cell Cardiol* 1990;22 (suppl V):45.

20 Sarajas HSS. Myocardial damage induced by immersion hypothermia. *Am J Cardiol* 1964;13:355–66.

21 Speicher CE, Ferrigan L, Wolfson SK, Yalav EH, Rawson AJ. Cold injury of myocardium and pericardium in cardiac hypothermia. *Surg Gynecol Obstet* 1962;114:659–65.

22 Tyers GFO, Williams EH, Huges HC, Todd GJ. Effect of perfusate temperature on myocardial protection from ischemia. *J Thorac Cardiovasc Surg* 1977;73:766–71.

23 Walter CA. Ultrastructural and functional changes in smooth muscle associated with freezing and thawing. In: Popovic V, Popovic P, eds. *Hypothermia in biology and medicine*. New York: Grune and Stratton, 1974:271–93.

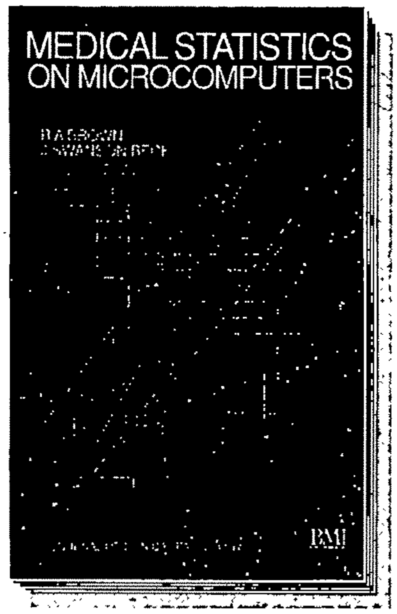
24 Maroko PR, Libby P, Covell JW, Sobel BE, Ross J, Braunwald E. Precordial S-T segment elevation mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. *Am J Cardiol* 1972;29:223–30.

25 Nikutta P, Haussmann D, Wenzlaff P. ST analysis: intragroup versus intrapatient variability of Holter results [abstract]. *J Am Coll Cardiol* 1989;13:189.

26 Bove EL, Stammers AH. Recovery of left ventricular function after hypothermic global ischemia: age-related differences in the isolated working rabbit heart. *J Thorac Cardiovasc Surg* 1986;91:115–32.

27 Corno AF, Bethencourt DM, Laks H, *et al*. Myocardial protection in the neonatal heart. *J Thorac Cardiovasc Surg* 1987;93:163–72.

28 Lamberti JJ, Cohn LH, Laks H, Braunwald NS, Collins JJ, Castaneda AR. Local cardiac hypothermia for myocardial protection during correction of congenital heart disease. *Ann Thorac Surg* 1975;20:446–54.



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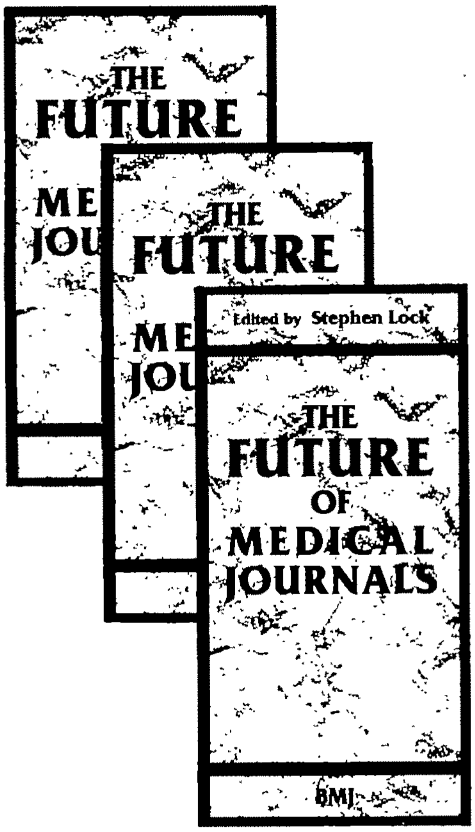

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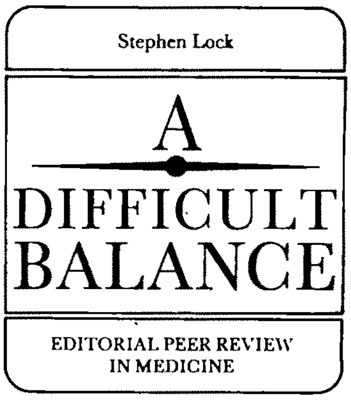
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A model to simulate the haemodynamic effects of right heart pulsatile flow after modified Fontan procedure

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Abstract

The effect of pulsatile pulmonary flow after the modified Fontan procedure was examined in a model that simulated the right heart. An inlet overflow tank (preload), axial pulsatile pump, Wind-Kessel model (afterload), and an outlet overflow tank were connected in series. The standard conditions were flow 2·00 l/min with 12 mm Hg preload pressure, 3·0 Wood units resistance, and an outlet overflow tank pressure at 6 mm Hg. The pump rate was set at 80 beats/min. The simulated pulmonary arterial pressure and pulmonary flow waves produced by this model closely resembled those obtained from patients who had undergone the modified Fontan procedure. All variables except the preload were fixed and changes in pulmonary flow were examined at preload pressures of 8, 12, 15, and 17 mm Hg. As the peak pulmonary arterial pressure increased so did pulmonary flow, until it was greater than during the non-pulsatile state. Because the afterload of this model was fixed, this result suggests that there was a concomitant decrease in resistance.

This model indicates that pulsatile pulmonary blood flow is likely to have a beneficial effect on the pulmonary circulation after the modified Fontan procedure.

After the modified Fontan procedure the right atrial and pulmonary arterial pressure waves, which are almost entirely a function of right atrial contraction and relaxation, have a characteristic configuration.[1-3] It has not known however, whether the pulsatile blood flow from the right heart has any effect on the pulmonary circulation. We studied this question in a model we constructed to simulate the right heart after the modified Fontan procedure.

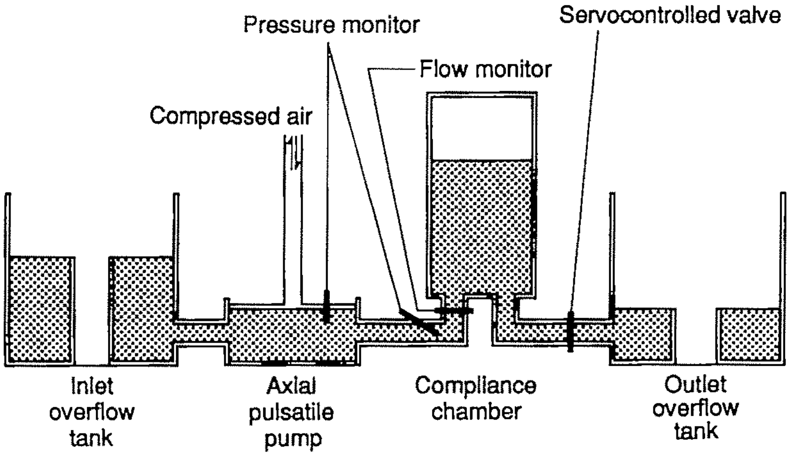

Figure 1 Simulation of the right heart after a modified Fontan procedure. The inlet overflow tank (preload), axial pulsatile pump, Wind-Kessel model (afterload), and the outlet overflow tank (left atrium) were connected in series and filled with water at 37°C.

Method

Figure 1 shows the model simulating the right heart after the modified Fontan procedure. The inlet overflow tank (preload), axial pulsatile pump, Wind-Kessel model (afterload), and the outlet overflow tank (left atrium) were connected in series and filled with water at 37°C. A rise in the level of the water in the inlet overflow tank was prevented by an open cylinder. The height of this cylinder determined the preload. In this model the axial pulsatile pump had no prosthetic valves in either the inlet or outlet parts to better reproduce conditions present in the right atrium after the modified Fontan procedure. The Wind-Kessel model, which provided the afterload, was constructed of a compliance chamber and a servocontrolled valve. The compliance chamber was filled with air to one third of its total volume.[4] The standard conditions were established in a non-pulsatile state: flow was 2·00 l/min with a 12 mm Hg preload, the afterload was 3·0 Wood units, and the outlet overflow tank pressure was 6 mm Hg. Afterload and outlet overflow tank pressures were fixed throughout the experiment. The pump was set at a rate of 80 beats/min. Under standard conditions this model produced pulmonary arterial pressures and pulmonary flow waves that resembled those recorded in a patient who had undergone the modified Fontan procedure (fig 2). The driving pressure, systolic fraction, and the vacuum were adjusted (while the standard conditions were maintained) to create a pulsatile flow that produced graduated increases peak pulmonary arterial pressures to values 1 mm Hg greater than the preload. This was done to examine the changes generated in the pulmonary flow waves. The same manipulations were performed at the other preload values of 8, 15, and 17 mm Hg.

We used a Sharp control air driving pump (H-4000). All fluid filled catheters were connected to Gould P-50 pressure transducers. The flow rate was measured electromagnetically with a Nihonkouden MFV-2100 flowmeter and a FF-150T cannulating flow

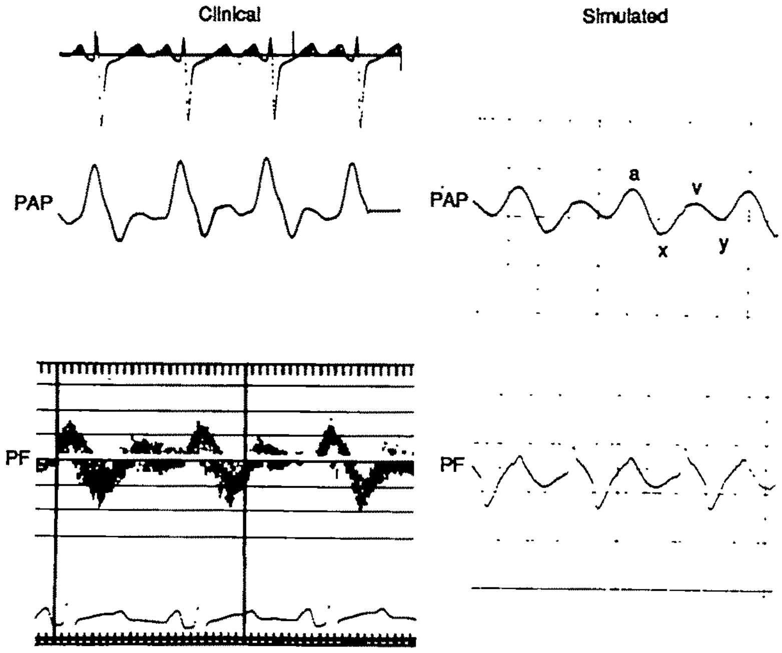

Figure 2 Clinical and simulated pulmonary arterial pressure (PAP) and pulmonary flow (PF) waves. Clinical PF waves were recorded by Doppler echocardiography. Simulated PAP and PF waves closely resemble the clinical examples.

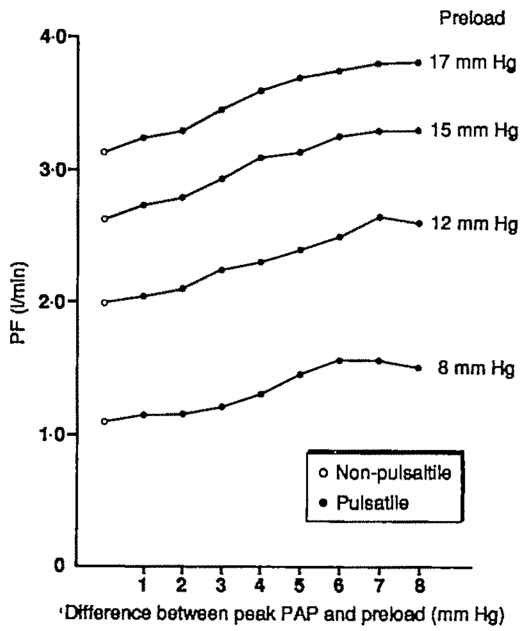

Figure 4 Changes in pulmonary flow (PF) examined at preloads of 8, 12, 15, and 17 mm Hg when all another variables remained constant. Each pulsatile flow pattern was produced by an increase in the peak pulmonary arterial pressure (PAP) in 1 mm Hg steps above the preload.

transducer. Pressure and flow signals were recorded on a San-ei 361 eight channel polygraph.

Results

Under standard conditions, with a 12 mm Hg preload, we simulated eight pulsatile flow patterns with peak pulmonary arterial pressures 1 mm Hg greater than the preload—that is 13, 14, 15, 16, 17, 18, 19, and 20 mm Hg when the preload was 12 mm Hg. We recorded pump pressure, pulmonary flow, pulmonary arterial pressure, and waves at each pressure (fig 3). These waves closely resembled clinical tracings. As peak pulmonary arterial pressure became increasingly greater than the preload, pulmonary flow increased from 2·00 l/min in the non-pulsatile state to a maximum of 2·65 l/min at a peak pulmonary arterial pressure of 19 mm Hg (fig 4). Changes in pulmonary flow were also seen when the preload was set at 8, 15, and 17 mm Hg (fig 4) and all other standard conditions were held constant. At any given preload there was a corresponding pulmonary arterial pressure that produced the greatest pulmonary flow. For an 8 mm Hg preload the largest pulmonary flow seen was 1·55 l/min at a peak pulmonary arterial pressure of 14 mm Hg. At a 15 mm Hg preload and 22 mm Hg peak pulmonary arterial pressure, pulmonary flow was 3·30 l/min. With a preload of 17 mm Hg and a peak pulmonary arterial pressure of 25 mm Hg, pulmonary flow was 3·80 l/min. Peak flow rates under non-pulsatile conditions for preloads of 8 mm Hg, 15 mm Hg, and 17 mm Hg were 1·10 l/min, 2·65 l/min, and 3·15 l/min respectively. Pulmonary flow when peak pulmonary arterial pressures were optimal was much greater than under non-pulsatile conditions.

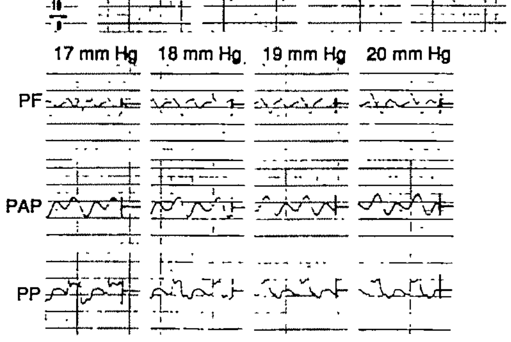

Figure 3 Non-pulsatile and pulsatile pulmonary flow (PF), pulmonary arterial pressure (PAP), and pump pressure (PP) waves under standard conditions: flow rate 2·00 l/min, with 12 mm Hg preload, resistance, 3·0 Wood units and an outlet overflow tank pressure of 6 mm Hg in a non-pulsatile state. As the peak PAP increased above the preload, the PF increased from 2·00 l/min in the non-pulsatile state to a maximum of 2·65 l/min at a peak PAP of 19 mm Hg.

Discussion

The results of clinical and experimental studies that examined the importance of atrial contraction in providing energy to the pulmonary circulation in patients after a modified Fontan procedure are conflicting. Yacoub reported that pulsatile pulmonary blood flow had a beneficial effect on gas exchange and affected the regulation of pulmonary vascular tone after this operation.[5] Using a velocity transducer Nakazawa *et al* showed that atrial contraction enhanced flow into the pulmonary circulation.[6] However, the results of several experimental[7 8] and clinical[9 10] studies suggest that atrial contraction may not be essential for the maintenance of the pulmonary and systemic circulations. Thus the importance of pulsatile pulmonary blood flow from atrial contraction after the modified Fontan procedure remains controversial.

Changes in the right heart can be difficult to evaluate in vivo because changes in the left heart can affect the right heart. In the present right heart model we directly investigated the haemodynamic effects of pulsatile pulmonary flow. The axial pulsatile pump in this model had a contraction characteristic that was linearly related to the afterload. When Lau *et al* studied the instantaneous pressure-volume relation of the right atrium during isovolumic contraction in the canine heart they found a straight line relation between the end systolic pressure and volume.[11] This suggests that the valveless axial pulsatile pump model may be able to simulate the haemodynamic effects of the right heart after the modified Fontan procedure. In fact, the pulmonary arterial pressure and pulmonary flow waves simulated in this model closely resemble the waveforms obtained from patients after the modified Fontan procedure. On the other hand, de Leval *et al*, using a similar system, reported that the introduction of pulsation predominantly increased the proximal venous pressure.[12] The reasons for the discrepancy between their results and ours is not clear. However, their report did not specify the pulsatile conditions or include the pulmonary artery pressure tracings. We believe that it is important that the simulated pulmonary arterial pressure trace mimics a clinical one before meaningful conclusions can be drawn. We found that the pulmonary arterial pressure trace was affected by the pump driving pressure, fraction of systole, and the vacuum. In fact, in our model, suboptimal pulsatile conditions produced poor pulmonary flow, resulting in pulmonary arterial pressure tracings that did not resemble clinical ones. Such suboptimal conditions might contribute to increased back flow rather than to forward flow. Whether one of these factors or some other factor is responsible for the discrepancy between our results and those of de Leval *et al* is not clear and requires further study.

Nevertheless, in our model when the pulsatile conditions were optimised to produce a pulmonary arterial pressure trace that mimicked a clinical one, we found that as the peak pulmonary arterial pressure increased, pulmonary flow gradually increased until it was greater than during the non-pulsatile state. The resistance in this model is fixed by the non-elastic tube. So an increase in pulmonary flow with pulsation suggests that pulsation decreases the resistance. These results suggest that pulsatile pulmonary blood flow has a beneficial effect on the pulmonary circulation after the modified Fontan procedure.

1 Serratto M, Miller RA, Tatooles C, Ardekani R. Hemodynamic evaluation of Fontan operation in tricuspid atresia. *Circulation* 1976;54(suppl III):99–101.
2 Ross DN, Somerville J. Surgical correction of tricuspid atresia. *Lancet* 1973;i:845–9.
3 Sanders SP, Wright GB, Keane JF, Norwood WI, Castaneda AR. Clinical and hemodynamic results of Fontan operation for tricuspid atresia. *Am J Cardiol* 1982;49: 1733–9.
4 Umezu M, Tomino T, Kawazoe K, *et al*. Mechanical simulator for the evaluation of hemodynamic performance of artificial heart valves. Mechanics in Medicine and Biology, Digest of 2nd international conference 1980: 136–7.
5 Yacoub MH. Fontan's operation—are caval valves necessary? In: Anderson RH, Shinebourne EA, eds. *Pediatric cardiology 1977*. Edinburgh: Churchill Livingstone, 1977:581–8.
6 Nakazawa M, Nakanishi T, Okuda H, *et al*. Dynamics of right heart flow in patients after Fontan procedure. *Circulation* 1984;69:306–12.
7 Shemin RJ, Herrill WH, Pfeifer JS, Conkle DM, Morrow AG. Evaluation of right atrial-pulmonary arterial conduits for tricuspid atresia—experimental study. *J Thorac Cardiovasc Surg* 1979;77:685–90.
8 Matsuda H, Kawashima Y, Takano H, Miyamoto K, Mori T. Experimental evaluation of atrial function in right atrium-pulmonary artery conduit operation for tricuspid atresia. *J Thorac Cardiovasc Surg* 1981;81:762–7.
9 Behrendt DM, Rosenthal A. Cardiovascular status after repair by Fontan procedure. *Ann Thorac Surg* 1980;29: 322–30.
10 Janos GG, Gelfand MJ, Schwartz DC, Kaplan S. Postoperative evaluation of the Fontan procedure by radionuclide angiography. *Am Heart J* 1982;104:785–93.
11 Lau VK, Sagawa K, Suga H. Instantaneous pressure-volume relationship of right atrium during isovolumic contraction in canine heart. *Am J Physiol* 1979;236: H672–9.
12 de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. *J Thorac Cardiovasc Surg* 1988;96:682–95.

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Determination of cardiac output by an angle and diameter independent dual beam Doppler technique in critically ill infants

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Abstract

***Objective*—To compare cardiac output measurements in critically ill infants by the dual beam Doppler and thermodilution techniques.**

***Design*—Prospective direct comparison of the two techniques. For statistical evaluation one randomly assigned paired measurement of every patient was used.**

***Setting*—Paediatric intensive care unit in a university hospital.**

***Patients*—18 infants after open heart surgery aged 4–25 months (weight 4–10 kg).**

***Interventions*—Cardiac output measurements by dual beam Doppler and thermodilution techniques were performed within 10 minutes of each other and without knowledge of the results of the other methods. Multiple measurements were performed on some patients with a pharmacological or electrophysiological intervention or with a minimum of six hours between each pair of measurements.**

***Measurements and main results*—Three patients were excluded because of an inadequate Doppler signal or a significant residual shunt. Cardiac output measurements ranged from 0·4 to 2·2 l/min for the thermodilution technique and from 0·5 to 2·1 l/min for the dual beam Doppler technique. Agreement between both methods was acceptable. The mean difference between the two methods was 0·026 l/min with two standard deviations ranging from − 0·20 to 0·26 l/min.**

***Conclusion*—The dual beam Doppler technique was shown to have promise for the non-invasive determination of cardiac output in critically ill infants.**

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Assessment of cardiac function is important in the evaluation and treatment of critically ill neonates, infants, and children. Cardiac output is usually measured by thermodilution or dye dilution techniques. These techniques, however, require insertion of a catheter into the pulmonary artery.[1-3] They are complicated in neonates and infants because the arteries small size and are associated with low but measurable morbidity and mortality. Pulsed Doppler measurement of cardiac output has been proposed as a non-invasive method of measuring cardiac output in children and in adults.[4-6] In critically ill patients technique was, however, reported to be unsatisfactory compared with the thermodilution method.[7 8] The following factors are thought to contribute to the inaccuracy of the Doppler method:

(*a*) Incorrect determination of vessel diameter, which is subsequently squared to calculate the cross sectional area of the vessel[5-8]—for example, measurement of the aortic diameter as 11 mm instead of 10 mm in a neonate causes overestimation of cardiac output by 21%. There are also appreciable changes in cross sectional areas of aortic and pulmonary arteries during the cardiac cycle—for example 9% and 12% respectively in dogs.[9]

(*b*) Velocity measurements when the angle of insonation (θ) is > 15° can significantly underestimate cardiac output, especially if a "blinded" technique is used in which a small angle θ is assumed.[5-8]

(*c*) Incorrect determination of the mean velocity by measurement of the velocity at only one point within the vessel. This velocity is used as the spatially averaged velocity assuming a flat velocity profile. It has been shown, however, that in both major arteries the velocity pattern changes.[10 11]

The dual beam Doppler system is supposed to avoid many of the limitations of cardiac output determination by conventional Doppler echocardiography[12-14] and a dual beam Doppler system is now available for infants and children. We have evaluated the accuracy of the dual beam device for measuring cardiac output in critically ill infants and children by comparing it with cardiac output measured by thermodilution.

Patients and methods

The study group consisted of 18 patients aged 4 to 25 months (mean 9·9 months) with a weight of 4·1 to 10 kg. The indication for cardiac output measurement by thermodilution was management after open heart surgery. Surgery included repair of an atrioventricular septal defect in four patients and closure of a ventricular septal defect in 11 patients. We repaired tetralogy of Fallot, double outlet right ventricle, and transposition of the great arteries in one patient each. The catheters were placed in during operation. Multiple measurements were made in some patients who had a pharmacological or electrophysiological intervention and in other patients who had a minimum of six hours between each pair of measurements.

DUAL BEAM DOPPLER TECHNIQUE:
PRINCIPLE OF OPERATION

A commercially available dual beam Doppler system (Quantascope, Vital Science) with a 4 MHz two element annular array transducer (paediatric probe) was used. The "attenuation compensated flowmeter"[15] used for this technique consists of a non-imaging, two parallel channel pulsed Doppler system with two concentric ultrasound beams and this approach has been described extensively.[12-14] Briefly, the first beam is a uniform wide beam, with a sample volume that totally encompasses the vessel lumen (fig 1). The second, a narrow beam, is wholly within the flowing blood and its area at any depth is known exactly. Because of the size of the narrow beam, the diameter of the ascending aorta should be at least 10 mm.

Mean velocity ($\overline{V}$) is measured with the wide beam, which completely insonates the ascending aorta and thus determines the Doppler shift frequency of all erythrocytes passing through the aorta. Thus a constant velocity profile does not have to be assumed; $\overline{V}$ is then proportional to the mean Doppler shift frequency ($\overline{Fd}$) divided by cos θ of the angle of insonation:

$$\overline{V} \propto \overline{Fd}/\cos\theta \qquad (1)$$

The cross sectional area of the ascending aorta (A) is calculated from the intensity of the returned Doppler shift frequencies of the two beams. Because each erythrocyte contributes equally to this backscattered Doppler power, the Doppler power of the wide beam (Pw) is equal to the projected lumen area (A_p) multiplied by an unknown attenuation constant (K_a):

$$P_w = A_p \times K_a \qquad (2)$$

Because A_p is equal to A divided by the cos θ, equation (2) can be written as:

$$P_w = \frac{A \times K_a}{\cos\theta} \qquad (3)$$

So in equation (2) the Doppler power of the narrow beam (P_n) equals the known area of the narrow beam (A_n) multiplied by the same attenuation constant K_a:

$$P_n = A_n \times K_a \qquad (4)$$

A combination of equations (3) and (4) gives the cross sectional area A as:

$$A = A_n \times \cos\theta \times \frac{P_w}{P_n} \qquad (5)$$

Cardiac output (CO) is the product of $\overline{V}$, A, and heart rate (HR). Therefore combination of equations (1) and (5) gives, cardiac output as:

$$CO = C \times A_n \times \overline{Fd} \times \frac{P_w}{P_n} \times HR \qquad (6)$$

where C is a precalibrated attenuation constant.

The dual beam Doppler technique determines Doppler shift frequency, Doppler power return of the two beams, and heart rate. Equation (6) is used to calculate cardiac output (fig 1). Cardiac output measurements by this device are independent of the angle of insonation θ and a separately determined cross sectional area.

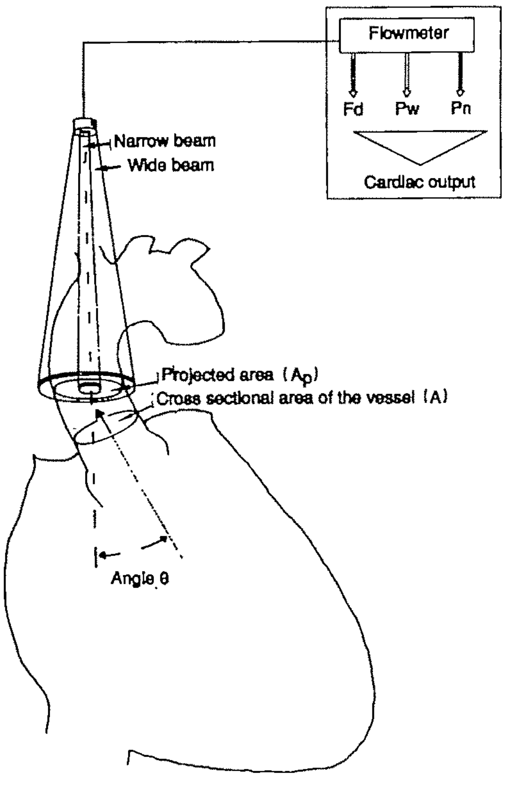

Figure 1 Schematic drawing showing the two beams of the dual beam Doppler in a front view of the heart and ascending aorta. Pn and Pw, returned Doppler power from the narrow and wide beams; Fd, mean Doppler shift.

DOPPLER CARDIAC OUTPUT MEASUREMENTS

The transducer was placed in the suprasternal notch and directed towards the ascending aorta. The transducer position and sample depth were optimised by the typical audio signal of aortic blood flow and by maximisation of the power return of the small beam. The power and velocity wave forms were evaluated with an online computer (Toshiba 3100). Dependent upon the heart rate of the patient, five to 15 beats were averaged and measurements of cardiac output, stroke volume, heart rate, and flow acceleration were obtained. The precision of cardiac output determination of the first 16 patients was limited to 0·1 l/min; with changed software it was improved to 0·001 l/min. Measurements were made without knowledge of the cardiac output by thermodilution.

MEASUREMENT OF CARDIAC OUTPUT
BY THERMODILUTION

Cardiac output was measured by thermal dilution within 10 minutes of the Doppler determination of cardiac output without knowledge of those results and in an unchanged haemodynamic state. The study protocol consisted of three iced dextrose injections, which were averaged. Computation of cardiac output was done either with an Abbot Oximetrix 3 cardiac output computer or with the cardiac output module of the Mennen Medical Solo monitor system. The precision of cardiac output determination was limnited to 0·1 l/min.

STATISTICAL ANALYSIS

For the statistical evaluation of the agreement between the measurements of cardiac output by thermodilution and dual beam Doppler techniques only one randomly assigned paired measurement of each patient was used. The mean of each pair of measurements, together with the difference between each pair, were determined and these were plotted against each other. Agreement between the two methods was estimated by calculating the mean difference between the two methods and two standard deviations (SD) as suggested by Bland and Altman.[16] The difference between the two measurements of each pair was evaluated in absolute values and also as a percentage of the average cardiac output of each pair:

$$\% \text{ difference} = \frac{\text{CO thermodilution} - \text{CO Doppler}}{(\text{CO thermodilution} + \text{CO Doppler}) \div 2} \times 100$$

Reproducibility studies in adults showed that a difference of at least 15% (with three determinations for one measurement) between successive measurements is necessary to indicate a significant change in cardiac output.[17] For that reason percentage differences of >15% between results from thermodilution and Doppler techniques were regarded as clinically meaningful.

To illustrate the whole scatter of differences, all pairs of measurements were also evaluated; although it is not total, these pairs show some independence because of the changes that occur in the patient's clinical state between each pair of measurements.

Results

Three of the 18 patients were excluded—two because of an inadequate Doppler signal. One of the two had a residual left ventricular outflow obstruction with high blood flow velocities that caused aliasing. The other had transposition of the great arteries. The third patient was excluded because of a significant residual shunt, as shown by colour Doppler echocardiography and by an increase in oxygen saturation from the right atrium to the pulmonary artery. This would have caused an overestimation of cardiac output by the thermodilution method.

We obtained 96 pairs of measurements from the remaining 15 patients. Cardiac output determinations ranged from 0·5 to 2·1 l/min for the Doppler technique and from 0·4 to 2·2 l/min for the thermodilution method.

In the 15 pairs of measurements used for statistical evaluation, an acceptable agreement was found between the two methods, with a mean difference of 0·026 (2SD range −0·20–0·26) l/min (fig 2). The mean percentage difference between the methods was 1·9% (2SD range −20·5–24·2)% (fig 3). In one patient the percentage difference was >15%. In four patients the percentage difference was borderline at about 15%.

When all 96 pairs of measurements were used similar results were obtained (table, figs 2 and 3). In 13 pairs of measurements the percentage difference was >15% and in another six this was borderline at about 15%.

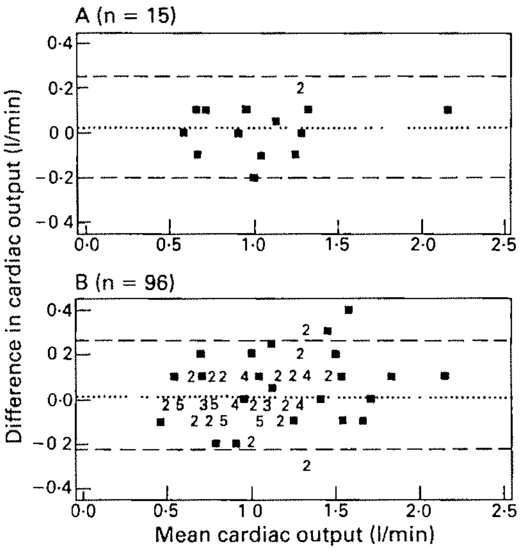

Figure 2 Differences in l/min between cardiac output determinations by thermodilution and Doppler plotted against the mean of the two determinations. (A) Only one randomly assigned paired measurement of every patient (n = 15) is shown. (B) All paired measurements (n = 96) are shown. Each square represents a measurement on one pair. Where two or more measurements fall on the same point they are indicated by the appropriate number.

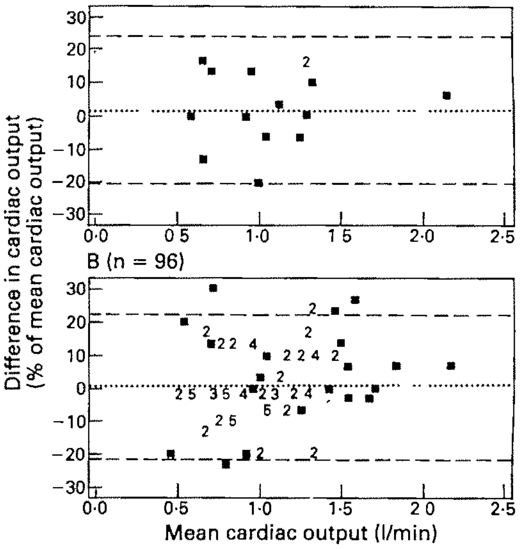

Figure 3 Differences between cardiac output determinations by thermodilution and Doppler as percentages of the mean of the two determinations plotted against that mean. Explanation as for fig 2.

Discussion

In the group of critically ill children studied, cardiac output measurements by the dual beam Doppler and thermodilution methods showed acceptable agreement. This is the first study to evaluate the dual beam Doppler method in critically ill children. In adults as good, or better, results have been reported with the dual beam Doppler system in patients during cardiac catheterisation and in medical or surgical intensive care units.[12-14] Two other studies in patients in intensive care found good correla-

Agreement between dual beam Doppler and with thermodilution technique

	Thermodilution v Doppler	
	One pair of measurements per patient (n = 15)	*All pairs of measurements (n = 96)*
Mean difference (2SD) (l/min)	0·026 (0·23)	0·018 (0·25)
Mean percentage difference (2SD) (%)	1·88 (22·36)	0·65 (22·37)

tions between cardiac output measured by the dual beam Doppler and thermodilution techniques. It was also noted that in some patients significant differences between the two methods could be shown by bias analysis.[18,19] In our study we found a considerable variation between results obtained by the two techniques: 95% of the percentage differences could be expected in the range −21% to 25%. In only one of the 15 paired measurements and in 13 of all paired measurements percentage differences >15% were found and these were considered to be clinically meaningful. In a recent study that compared cardiac output measured by conventional Doppler echocardiography and by thermodilution in critically ill children a percentage difference >15% between the two methods was noted in 45% of all measurements and a percentage difference >25% was evident in a quarter of the measurements.[7] Compared with these results the dual beam Doppler technique seems to give a more reliable measure of cardiac output in critically ill children. This is probably owing to the elimination of possible errors of the conventional Doppler method, as mentioned previously. The accuracy of the dual beam Doppler technique could probably be increased by averaging three measurements as in the thermodilution technique. In this technique the difference between two successive determinations necessary to show a significant change in cardiac output can be reduced from 26% to 15% if an average of three measurements is taken.[17]

None the less the accuracy of the thermodilution method in humans is not known exactly and minor alterations in technique can cause overestimation of cardiac output by as much as 58%.[20,21] Even under optimum conditions in vitro the standard error is seldom less than 10%.[22] In a recent reproducibility study only 70% of the differences were within 20% of the mean value.[23] It has been concluded that the overall biological error of any method of cardiac output measurement is 15–20%.[24]

Both Doppler methods, when used from the supersternal notch, calculate cardiac output without coronary blood flow. This explains, at least to some extent, the underestimation of Doppler cardiac output measurements compared with the thermodilution method in this study. Furthermore, the thermodilution method might have overestimated cardiac output because of small residual shunts that are often present immediately after patch closure of ventricular septal defects and which subsequently close spontaneously.[25] For most of our patients colour Doppler echocardiography was not available in the early postoperative period. Colour Doppler echocardiography carried out later showed a residual shunt only in the one patient mentioned earlier, who was excluded from the study population.

The dual beam Doppler method is subject to several systematic errors. Unless the wide beam completely insonates the aorta cardiac output will be underestimated. Similarly the sample volume of the narrow beam has to be completely within the aorta, otherwise overestimation results. Furthermore, the wide beam may not reach the complete ascending aorta because of overlying lung tissue. On the other hand, the main or right pulmonary artery may also be partly insonated by the wide beam. Both of these factors will cause errors in calculated cardiac output. Because the Doppler power return of the two beams is used to calculate aortic cross sectional area, this calculation, as with conventional Doppler echocardiography, seems to be a source of possible major errors. The problem may be aggravated when the dual beam Doppler technique is used over the whole paediatric age group. Another Doppler probe with larger sized beams may be needed for older children who are still too small for the adult probe. Premature infants with low and very low birth weight need a probe with even smaller beams.

We concluded that the dual beam Doppler technique is a simple and promising method to measure the ascending aortic blood flow non-invasively in critically ill infants. It seems especially useful in this age group, in which invasive cardiac output measurement is more difficult than in older children or the adult population. Further evaluation of this system including its use in older children is needed.

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1 Pollack MM, Reed TP, Holbrook PR, Fields AI. Bedside pulmonary artery catheterization in pediatrics. *J Pediatr* 1980;96:274–5.

2 Swedlow DB. Invasive assessment of the failing circulation. In: Swedlow DB, Raphaely RC, eds. *Cardiovascular problems in pediatric critical care.* New York: Churchill Livingston, 1986:112–49.

3 Tabata BK, Kirsch JR, Rogers MR. Diagnostic tests and technology for pediatric intensive care. In: Rogers MR, ed. *Textbook of pediatric intensive care.* Baltimore: Williams and Wilkins, 1987:1401–32.

4 Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. *J Pediatr* 1982;101: 46–50.

5 Goldberg SJ, Sahn DJ, Allen HD, Valdes-Cruz LM, Hoenecke H, Carnahan Y. Evaluation of pulmonary and systemic blood flow by two-dimensional Doppler echocardiography using Fast Fourrier transform spectral analysis. *Am J Cardiol* 1982;50:1394–9.

6 Huntsman LL, Steward DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler Determination of cardiac output in man. Clinical validation. *Circulation* 1983;67:593–602.

7 Notterman DA, Castello FV, Steinberg C, Greenwald BM, O'Loughlin JE, Gold JP. A comparison of thermodilution and pulsed Doppler cardiac output measurement in critically ill children. *J Pediatr* 1989;115:554–60.

8 Donovan KD, Dobb GJ, Newman MA, Hockings BES, Ireland M. Comparison of pulsed Doppler and thermodilution methods for measuring cardiac output in critically ill patients. *Crit Care Med* 1987;15:853–7.

9 Loeber CP, Goldberg SJ, Marx GR, Carrier M, Emery RW. How much does aortic and pulmonary areary area vary during the cardiac cycle? *Am Heart J* 1987;113:95–100.

10 Redel DA. *Color blood flow imaging of the heart.* Berlin, Heidelberg, New York: Springer, 1989:31–42.

11 Jenni R, Vieli, A, Ruffmann K, Krayenbühl HP, Anliker M. A comparison between single gate and multigate ultrasonic Doppler measurements for the assessment of

the velocity pattern in the human ascending aorta. *Eur Heart J* 1984;5:948–55.

12 Evans JM, Skidmore R, Luckman NP, Wells PNT. A new approach to the noninvasive measurement of cardiac output using an annular array Doppler technique—I. Theoretical considerations and ultrasonic fields. *Ultrasound Med Biol* 1989;15:169–78.

13 Evans JM, Skidmore R, Baker JD, Wells PNT. A new approach to the noninvasive measurement of cardiac output using an annular array Doppler technique—II. Practical implementation and results. *Ultrasound Med Biol* 1989;15:179–87.

14 Looyenga DS, Liebson PR, Bone RC, Balk RA, Messer JV. Determination of cardiac output in critically ill patients by dual Doppler echocardiography. *J Am Coll Cardiol* 1989; 13:340–7.

15 Hottinger CF, Meindl JD. Blood flow measurement using the attenuation compensated volume flow meter. *Ultrason Imaging* 1979;1:1–15.

16 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.

17 Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Respir Dis* 1982;126:1001–4.

18 Niclou R, Teague SM, Lee R. Clinical evaluation of a diameter sensing Doppler cardiac output meter. *Crit Care Med* 1990;18:428–32.

19 Wong DH, Mahutte CK. Two-beam cardiac output measurement: reproducibility and agreement with thermodilution. *Crit Care Med* 1990;18:432–7.

20 Mārushak GF, Potter AM, Schauble JF, Rogers MC. Overestimation of pediatric cardiac output by thermal indicator loss. *Circulation* 1982;65:380–3.

21 Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output: comparison with a non golden standard. *Am J Cardiol* 1984;53:257–9.

22 Mackenzie JD, Haitres NE, Rawles JM. Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers. *Br Heart J* 1986;55:14–24.

23 Russell AE, Smith SA, West MJ, Aylward PE, McRitchie RJ, Hassam RM, *et al*. Automated non-invasive measurement of cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution and thermodilution. *Br Heart J* 1990;63:195–9.

24 Levitt JM, Replogle RL. Thermodilution cardiac output: a critical analysis and review of the literature. *J Surg Res* 1979;27:392–404.

25 Stevenson JG, Kawabori I, Stamm SJ, Bailey WW, Hall DG, Mansfield PB, *et al*. Pulsed Doppler echocardiographic evaluation of ventricular septal defect patches. *Circulation* 1984;70(suppl I):38–46.

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Percutaneous transarterial balloon dilatation of the mitral valve: five year experience

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Abstract

***Objective*—To examine the value of transarterial balloon dilatation of the mitral valve for treatment of patients with mitral stenosis over a period of five years.**

***Design*—Analysis of patients' functional state, and haemodynamic and echocardiographic variables, before and immediately after the procedure and during a follow up of up to five years.**

***Setting*—A cardiovascular centre in Belgrade, Yugoslavia.**

***Patients*—Two hundred and ninety four patients who underwent percutaneous transarterial dilatation of the mitral valve between February 1985 and February 1990.**

***Results*—Mean mitral valve area was enlarged by 109%. Complications included death (0·7%), severe mitral insufficiency (2·3%), mild mitral insufficiency (9·9%), cerebral embolism (2%), and injury to the femoral artery (2%). Two more patients died at two and 11 months after the procedure. Late cardiac surgery was needed in eight patients (mitral insufficiency in three, restenosis in three, thrombus in one, and endocarditis in one. Restenosis occurred in seven patients. Four of these underwent repeat dilatation and three had surgery. Improvement of symptoms was seen in 94% of patients during the follow up.**

***Conclusion*—Transarterial balloon dilatation of the mitral valve gave good results with acceptable morbidity and mortality and had some advantages over the anterograde approach.**

Balloon dilatation of the mitral valve is often used to treat mitral valve stenosis. The original transvenous technique reported by Inoue *et al*[1] has been modified by many workers.[2 3] To avoid injuring the interatrial septum with large balloon catheters and to enable better stabilisation of the balloon across the mitral valve we started to use the transarterial approach in February 1985. This study describes our five year experience with this technique in 294 patients.

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Patients and methods

PATIENTS

From February 1985 to February 1990, 294 patients (238 (81%) women and 56 (19%) men aged 15–76 (mean (SD) 36 (7) years) underwent transarterial balloon dilatation of the mitral valve. Atrial fibrillation was present in 64% of patients. Only 35 patients (12%) had been given anticoagulants before the procedure. Sixty one patients were in the New York Heart Association (NYHA) functional class IV, 185 in class III, 37 in class II, and 11 in class I (all young women who wished to become pregnant). According to the echocardiographic criteria[4] 171 (58%) patients had a pliable mitral valve. There was calcification of the mitral valve or mitral apparatus or both, as verified by echocardiography and fluoroscopy, in 49 patients (16%) although 15 still had a pliable valve.

None of the patients had important coronary artery disease, 48 had aortic valve regurgitation of less than Sellers[5] grade III, two had considerable and four minor aortic valve stenosis. Nine patients had undergone previous open or closed mitral commissurotomy.

Patients with left atrial thrombi or mitral valve regurgitation greater than grade II and those with a significant iliofemoral arterial disease were excluded. All patients gave informed consent.

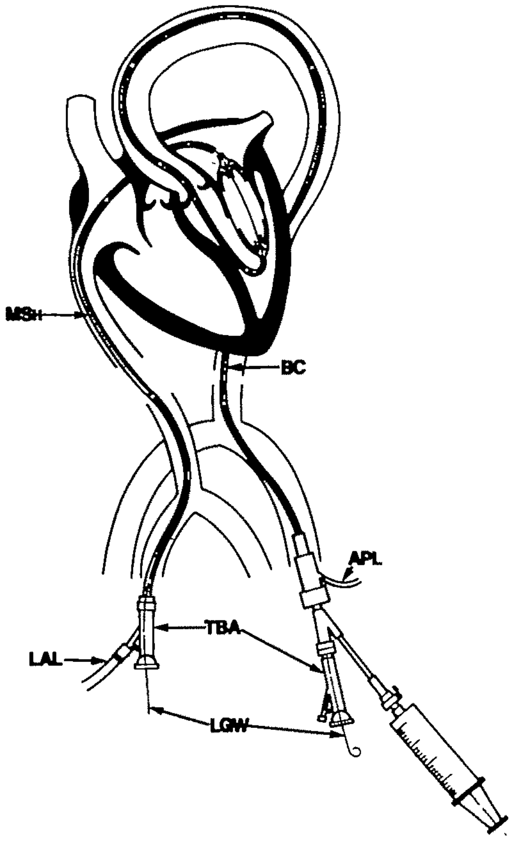
TECHNIQUE

The technique of transarterial balloon dilatation of the mitral valve has been reported previously.[6 7] A description of our present technique is given here. The double balloon catheter technique has not been used since low profile single catheter with the shaft connected to two balloons in parallel (twin Mansfield) became available.

Right and left catheterisations were performed. Cardiac output was determined by the Fick principle based on an assumed oxygen consumption[8] and by the thermodilution technique. The mitral valve area was calculated from the Gorlin formula.[9] Coronary angiography was performed in all patients to exclude those with coronary artery disease and to look for possible neovascularisation of left atrial thrombi.[10] A Mullins 8 French trans-septal sheath was advanced from the right femoral vein trans-septally into the left atrium. Heparin (100 units/kg) was given. A 7 French retrieval catheter[7] was advanced through a sheath from the left femoral artery to the aortic root where its wire loop was opened. A 7 French floating Swan-Ganz catheter (Vygon), which permits a 0·035 inch wire to pass through its central lumen, was advanced through the Mullins sheath into the left atrium. The Swan-Ganz floating catheter was inflated with carbon dioxide and advanced through the left ventricle into the aortic root across the wire loop of the retrieval catheter. A guide wire (350 cm long 0·035 inch diameter, with flexible J end, Cook) was advanced via the Swan-Ganz floating catheter from the right femoral vein into the aortic root where it was snared by the retrieval catheter and brought out of the body through the left femoral artery. A F14 sheath was inserted over this wire into the left femoral artery. A balloon catheter (twin Mansfield) was introduced over the wire through the F14 sheath from the left femoral artery to the aortic root. The floating catheter was withdrawn and a two way Tuohy-Borst adapter was attached on the proximal hub of the Mullins sheath. The central channel of the adapter secured the venous end of the long guide wire while the sidearm served as the left atrial line for monitoring of left atrial pressure and for simultaneous injection of contrast medium into the left atrium. The long guide wire was pushed from both sides to form a large loop within the left ventricle. The balloon catheter was advanced over the loop into the left ventricle up to 2–3 cm from the apex after which it was placed across the mitral valve by pulling the long guide wire from the venous side while the arterial end of the long wire was secured to the balloon catheter shaft by a Y connector (fig 1).

After the balloon was positioned across the valve orifice it was inflated and optimal positioning of the balloon was controlled by injection of contrast medium into the left atrium (30 ml volume; 8 ml/s flow). To keep the balloon stable, the Mullins sheath was pushed while the balloon catheter (secured to the wire by Y connector) was pulled forward (fig 2). The balloon was deflated and pulled back into the aortic root.

Figure 1 Diagram of transarterial balloon dilatation of the mitral valve. Note the tip of the Mullins sheath put into the left atrium during balloon inflation. APL, arterial pressure line from the sidearm of the introducer sheath; BC, balloon catheter; LAL, left atrial line; LGW, long guide wire; MSH, Mullins sheath; TBA, Tuohy-Borst two-way adapter.



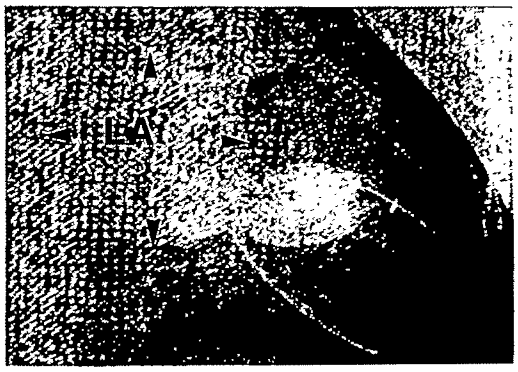


Figure 2 Cineangiogram showing a twin balloon (18 + 20 mm Mansfield) placed and semi-inflated across the mitral valve.

A single 25 mm balloon (Mansfield) was used in 17 patients, two balloons (2 × 18, 18 + 20, 2 × 20 mm Mansfield) in 188, and a bifoil (2 × 19 Schneider) or a "twin" (18 + 20) in 89 patients.

Left atrial pressure and the mitral gradients were recorded by advancing the Mullins sheath into the left ventricle and withdrawing it into the left atrium. When necessary, dilatation was repeated with the same or a larger balloon exchanged over the wire. The haemodynamic measurements and left ventriculography were repeated after final dilatation and in most patients contrast medium was injected into the left atrium through a pigtail catheter in the Mullins sheath to exclude left-right shunting. Cephalosporin was given intravenously one hour before and for the first 24 hours after the procedure. An oral antibiotic was given for the next five days. Oral anticoagulants were given to all patients for six months after balloon dilatation and treatment was continued for longer in those with atrial fibrillation. Balloon sizes were chosen according to diastolic left ventricular diameter, valve anatomy, and the body surface area.

FOLLOW UP

The patients were followed up as outpatients one and six months after the procedure and thereafter once a year. Clinical state and chest x ray film were assessed and physical examination and cross sectional and Doppler echocardiography were performed at each visit. Repeat catheterisation was performed only in patients with significant recurrent symptoms.

DATA ANALYSIS

Data were expressed as a mean (SD). The variables were compared by Student's t test.

Results

Within the five year period 16 patients with mitral stenosis were found to have left atrial thrombi and were sent for surgery rather than balloon dilatation of the valve. Transthoracic echocardiography showed atrial thrombi in 11

Haemodynamic results before and after percutaneous transarterial balloon dilatation of the mitral valve in 294 patients

	Before mean (SD)	*After mean (SD)*	*p Values*
Pressures (mm Hg):			
Pulmonary artery			
Systolic	62 (12)	44 (8)	<0·001
Mean left atrial	23 (6)	11 (4)	<0·001
Mean mitral valve gradient	18 (6)	6 (3)	<0·001
Cardiac output (l/min)	4·1 (0·7)	4·3 (0·6)	>0·05
Mitral valve area (cm^2)	1·1 (0·3)	2·3 (0·4)	<0·001

patients, and coronary angiography detected neovascularisation of thrombi in eight, including five in whom echocardiography had been negative. Thrombi were found at operation in all of these patients. In four patients transseptal catheterisation caused a haemopericardium and cardiac tamponade that required subxiphoid pericardiocentesis with a pigtail catheter. These patients were discharged and the procedure was successfully repeated two to four months later. Valve dilatation was accomplished in all 294 patients in whom it was attempted. The time needed for the entire procedure with a single balloon catheter (bifoil or twin) was less than one hour in most patients. In 14 patients the result was poor (enlargement of the mitral valve area was less than 25%).

The table gives the haemodynamic indices before and after balloon dilatation. The mean mitral valve area was enlarged by 109%. The increase in valve area was more prominent in younger patients and in those with a pliable valve (fig 3). In two patients with concomitant aortic valve stenosis, combined aortic and mitral valve balloon dilatation was performed with the same long guide wire arrangement.[11] The aortic valve gradients were reduced from 85 to 25 mm Hg and 110 to 50 mm Hg in these two patients. Aortic valve insufficiency grade II was produced in both.

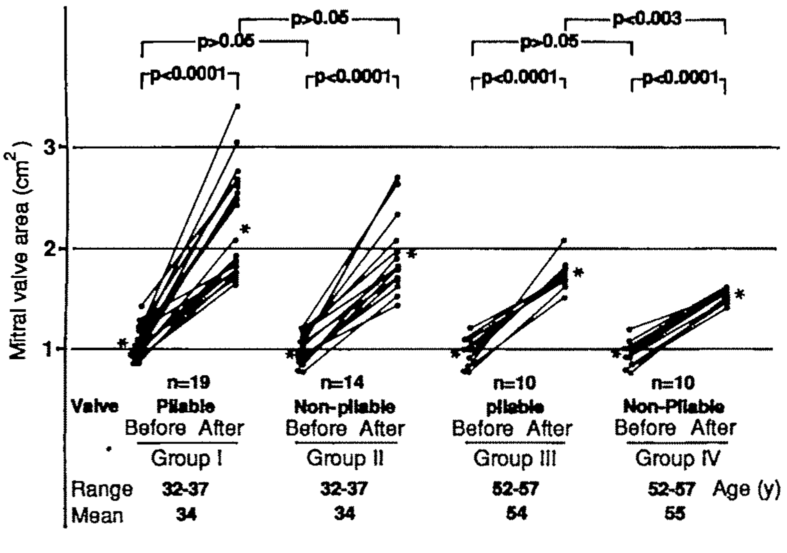


Figure 3 Individual values for mitral valve area before and after dilatation in 53 patients. All patients were dilated with the same 18 + 20 mm twin Mansfield balloon. Two age groups (range five years) were compared. The achieved enlargement of the mitral valve area was higher in younger patients and in those with a pliable valve.

COMPLICATIONS

There were two procedural deaths. One patient died of cerebral embolism and one of left coronary artery embolism. Cerebral embolism occurred in five further patients, only one of whom recovered completely. In all seven patients with embolic complications the transthoracic echocardiography had given inconclusive findings due to inadequate echogenicity, and transoesophageal echocardiography was not available at that time. Immediate surgery was needed in three patients because of acute severe mitral insufficiency, and at operation a tear in the anterior mitral leaflet was found in all of them. Four patients with post procedural grade III mitral insufficiency were discharged in a stable clinical condition. The left ventricular apex was perforated in one patient because the balloon was advanced too rapidly through the left ventricle. After pericardiocentesis and successful dilatation of the valve the perforation site had to be sutured surgically. Oximetry and opacification of the left atrium showed no left to right shunting after the dilatation in any of the 294 patients.

Vascular surgical intervention on the femoral artery was needed in seven patients (femoral artery intimal flap in three, bleeding at the puncture site in two, a clot in one, and a haematoma in one patient). Surgical intervention was sucessful in all seven patients and there were no chronic circulatory sequelae.

RESULTS AT FOLLOW UP

At one to three months after operation echocardiography confirmed poor results in 14 patients, whose symptoms remained unchanged. A review of the cineangiograms and video tapes of the procedures showed that in 11 of 14 patients the balloon had not been properly stabilised during inflation and the valve had not been dilated. Six of these patients underwent surgery. Commissural splitting was not found in any of them. In the other five patients balloon dilatation was repeated. These 14 patients were treated in the early part of our experience when simultaneous injection of contrast into the left atrium was not performed.

Two patients died (two and 11 months after operation). One of these patients had developed mitral regurgitation of grade II severity, and the other had no complication related to the operation.

Elective surgery was needed in three out of four patients with grade III mitral regurgitation. Surgery was performed at one year, 18 months, and two years after balloon dilatation. In two of these patients a tear in the anterior mitral leaflet was found and in the third the mitral annulus was dilated (perhaps as a result of overdilatation with 2 × 20 mm balloons). One patient was operated on because of a left atrial thrombus at two years, and one because of mitral endocarditis three months after balloon dilatation.

Restenosis (loss of more than 50% of the increase in valve area), as assessed by repeat catheterisation, was found in seven patients between six months and two years of follow up. Three had surgery and four had repeat balloon

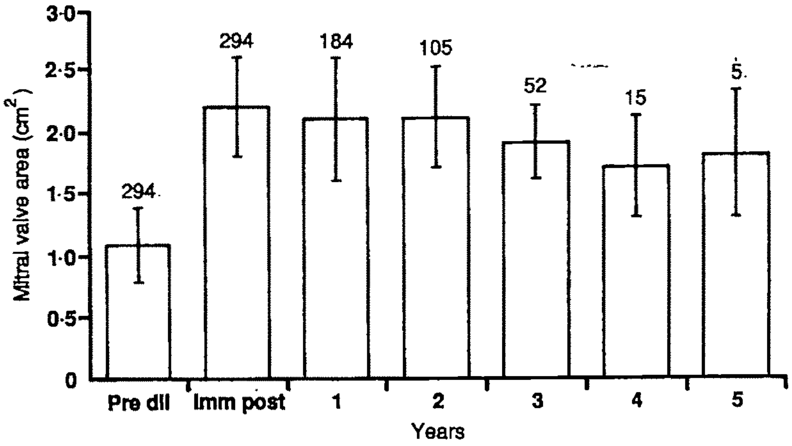


Figure 4 Mitral valve area as determined by cross sectional echocardiography before, (Pre dil) immediately after (Imm post), and one to five years after balloon dilatation of the mitral valve.

dilatation of the valve. In 19 patients atrial fibrillation was converted to sinus rhythm four to 15 (mean 5 (SD 4)) months after dilatation.

The cardiothoracic ratio decreased after the first six months from 0·5 (0·09) to 0·46 (0·1) ($p < 0·05$) in 210 patients and did not change further during follow up. Peripheral systemic emboli occurred in four patients during follow up but these had no serious sequelae. Cross-sectional echocardiography showed persistence of the achieved mitral valve area during follow up (fig 4). Symptoms improved in most patients during the five year period after balloon dilatation (fig 5). By three years after operation four patients returned to New York Heart Association class IV. Three of them underwent mitral valve replacement and one mitral and aortic valve replacement.

Discussion

This study reports our experience with transarterial balloon dilatation of the mitral valve in 294 patients, most of whom were young and had a favourable valve anatomy. The procedural mortality of 0·7%, 2·3% incidence of severe mitral regurgitation, and 2% incidence of embolism were similar figures to those reported after a transvenous approach.[12-14] With the advent of transoesophageal echoradiography, which became available in our hospital only in 1991, the risk of embolism should decrease because of better detection of atrial thrombi. There was local injury of the femoral artery in 2% of our patients. This complication is specific to the transarterial approach and it is regarded as the major disadvantage of this technique.

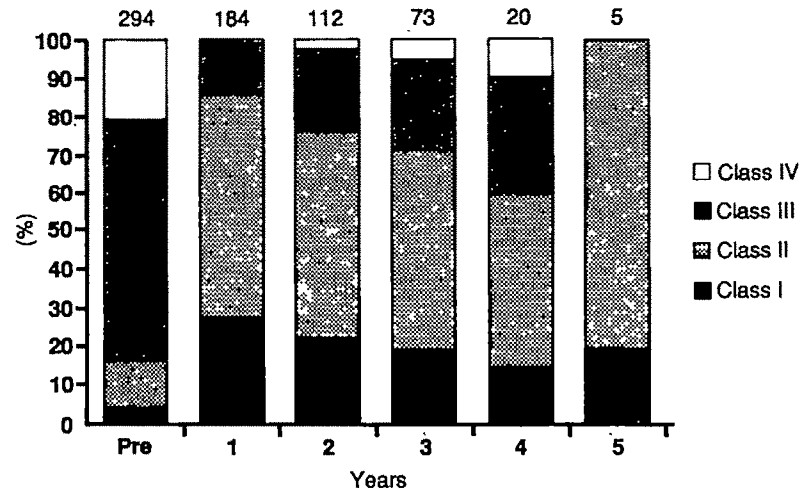


Figure 5 Changes of New York Heart Association functional classes after balloon dilatation of the mitral valve over a five year period.

The atrial septum may be damaged after balloon dilatation of the mitral valve. Although there have been reports that significant left to right shunting leads to an acquired Lutembacher syndrome,[15 16] it is generally considered that these shunts are of little haemodynamic importance. Left to right shunting was found in 62% of patients immediately after transvenous balloon dilatation with two balloons and in 48% of patients at six months after the procedure.[17] After the Inoue mitral balloon procedure left to right shunting, as detected by Doppler colour flow imaging, was found in 15% of patients immediately after and in 4% of patients one year after the procedure.[18] With the transarterial approach the balloon does not cross the atrial septum and damage to the septum is minimised. We found no evidence of left to right shunting in any of our 294 patients by oximetry. Petrossian *et al* calculated the mitral valve area after transvenous balloon dilatation of the mitral valve in 13 patients before and after occlusion of the septal hole with a balloon.[19] The calculated area was larger before than after occlusion. Even when oximetry does not show important shunting the calculated area after transvenous balloon dilatation of the mitral valve may overestimate the real area because of the atrial communication. This finding may mean that some reported data on transvenous balloon dilatation of the mitral valve may not be accurate because the calculation was done without the occlusion of the atrial septal hole.

The transarterial approach aids stabilisation of the ballons at the valve orifice during dilatation. Also simultaneous opacification of the left atrium monitors the events during the balloon inflation and avoids the false impression of valve dilatation that may occur when a resistant orifice causes ejection of the balloons from the orifice.

The major advantages of the transarterial approach are avoidance of injury to the atrial septum and good positioning of the balloon at the orifice. The Inoue balloon dilatation system, however, offers similar advantages and is easier to perform. The Inoue procedure must be compared with the transarterial approach to judge which technique is better.

Most of our patients experienced a symptomatic improvement that was maintained over the follow up period of up to five years. The results of this study support the use of balloon dilatation of the mitral valve for patients with mitral stenosis and pliant valves.

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1 Inoue K, Owaki T, Nakamura T, Kitamura F, Miymoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;87:394–402.

2 Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;313:1515–8.

3 Zaibag M, Ribeiro PA, Kasab S, Fagih MR. Percutaneous double balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet* 1986;i:757–61.

4 Palacios A, ed. *Atlas of 2-dimensional echocardiography*. New York: York Medical Books, 1983:93.

5 Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardiac angiography in acquired cardiac disease. Technic indication and interpretation in 700 cases. *Am J Cardiol* 1964;14:437–47.

6 Babic UU, Pejcic P, Djuristic Z, Vucinic M, Grujicic S. Percutaneous transarterial balloon valvuloplasty for mitral valve stenosis. *Am J Cardiol* 1986;57:1101–4.

7 Babic UU, Dorros G, Pejcic P, *et al.* Percutaneous mitral valvuloplasty: retrograde, transarterial double-balloon technique utilizing the transseptal approach. *Cathet Cardiovasc Diagn* 1988;14:229–37.

8 LaFarge CG, Miettinen OS. The estimation of oxygen consumption. *Cardiovas Res* 1970;4:23–30.

9 Carabello BA, Grossman W. Calculation of stenotic valve orifice area. In: Grossman W, ed. *Cardiac catheterization and angiography*. Philadelphia: Lea and Fibiger, 1986: 143,154.

10 Hubbard WN, Hine AL, Rubens M, Donaldson RM. Visualization of left atrial thrombi by coronary arteriography. *Cathet Cardiovasc Diagn* 1987;13:22–5.

11 Medina A, Bethencourt A, Coello I, *et al.* Combined percutaneous mitral and aortic valvuloplasty. *Am J Cardiol* 1989;64:620–4.

12 Ruiz CE, Alen JW, Lau FYK. Percutaneous double-balloon valvotomy for severe rheumatic mitral valve stenosis. *Am J Cardiol* 1990;65:473–7.

13 Nobuyoshi M, Hamasaki N, Kimura T, *et al.* Indications, complications, and short-term clinical outcome of percutaneous transvenous mitral commissurotomy. *Circulation* 1989;80:782–92.

14 Vahanian A, Michel PL, Cormier B, *et al.* Results of percutaneous mitral commissurotomy in 200 patients. *Am J Cardiol* 1989;63:847–52.

15 Goldberg N, Roman CF, Cha SD. Right to left interatrial shunting following balloon mitral valvuloplasty. *Cathet Cardiovasc Diagn* 1989;16:133–5.

16 Sadaniantz A, Luttmann C, Shulman RS, Block PC, Schachne J, Thompson PD. Acquired Lutembacher syndrome or mitral stenosis and acquired atrial septal defect after transseptal mitral valvuloplasty. *Cathet Cardiovasc Diagn* 1990;21:7–9.

17 Cequier A, Bonan R, Serra A, *et al.* Left-to-right shunting after percutaneous mitral valvuloplasty. *Circulation* 1990; 81:1190–7.

18 Ishikura F, Nagata S, Yasuda S, Yamashia N, Miyatake K. Residual atrial septal perforation after percutaneous transvenous mitral commissurotomy with Inoue balloon catheter. *Am Heart J* 1990;120:873–8.

19 Petrossian GA, Ziskin AA, Tuscu ME, Block PC, Palacios I. Atrial septal occlusion improves the accuracy of valve area determination following mitral balloon valvotomy [abstract]. *Circulation* 1990;82 (suppl III):498.

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CASE REPORT

Peripartum cardiomyopathy with recovery in a patient with coincidental Eisenmenger ventricular septal defect

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Abstract

Severe pulmonary vascular disease was found during pregnancy in a 31 year old woman with a large ventricular septal defect. Three months after delivery peripartum cardiomyopathy with severe biventricular failure developed. This was a chance association. Recovery of ventricular function was slow but was complete two years later. There was no advance in the pulmonary vascular disease.

Case report

A 31 year old Indian woman was found to have a systolic murmur in the antenatal clinic during the tenth week of her first pregnancy. She gave no cardiac history and did not report any limitation of exercise capacity. She was referred to the cardiology clinic where she was found to be acyanotic with normal venous pressure, right ventricular heave, pulmonary ejection click, and loud "single" second sound—signs of pulmonary hypertension associated with a large ventricular septal defect. The absence of cyanosis implied that the shunt was dominantly left to right. Chest *x* ray showed that her heart was only slightly increased by enlargement of the right atrium and of the proximal pulmonary arteries (fig 1A). The electrocardiogram showed sinus rhythm with right axis deviation and right ventricular hypertrophy. Cross sectional and Doppler echocardiography showed a large subaortic ventricular septal defect with obligatory pulmonary hypertension at systemic level. Both the left and right ventricles showed normal function; neither was enlarged (fig 2). There was little evidence of flow and no turbulence across the ventricular septal defect. Despite some concern about the risk to the mother of accelerating pulmonary vascular disease, her pregnancy proceeded uneventfully except for the development of pregnancy diabetes needing insulin. She had a haemoptysis at 35 weeks attributed to the pulmonary hypertension ("pulmonary apoplexy"). At that time oximetry showed 95% saturation, her arterial PO_2 was 11·0 kPa and the chest *x* ray was clear. A healthy female infant weighing 2·8 kg was delivered by elective lower segment caesarean section at 37 weeks. There were no complications. She was well on discharge and the physical signs were unchanged.

She remained well for three months after delivery but then became increasingly short of breath with cyanosis and swelling of her legs and hands. Physical examination showed new intense central and peripheral cyanosis. The blood pressure was 80/60 mmHg, her jugular venous pressure was raised at 8 cm and she had developed an apical third heart sound with a loud pansystolic murmur at the left sternal edge and apex attributed to atrioventricular valve regurgitation. Her chest *x* ray showed that her heart had become enlarged (fig 1B). There was now a right ventricular "strain" pattern on the electrocardiogram with T inversion. Her echocardiogram showed new global impairment of right and left ventricular function (fig 2). At cardiac catheterisation (table) there was bidirectional but predominantly right to left shunting at ventricular level ($\dot{Q}p/\dot{Q}s = 0{\cdot}76 : 1$) with equal left and right ventricular pressures and pulmonary hypertension at the systemic level. After inhalation of a high inspired oxygen content for ten minutes there was a shift to predominantly left to right shunting with a rise in aortic saturation from 75 to 89% ($\dot{Q}p/\dot{Q}s = 1{\cdot}17 : 1$), implying a degree of reactivity of the pulmonary vascular bed. Angiography confirmed the large ventricular septal defect. There was severe global impairment of right and left ventricular function. Her coronary arteries were normal. Three biopsy specimens were taken of the left ventricle. Histological examination (including electron microscopy) showed no recognisable abnormality. Viral studies and tests for autoantibodies were negative and thyroid function and vanillyl mandelic acids were normal.

Peripartum cardiomyopathy was diagnosed. Despite treatment with digoxin, diuretics, and captopril her condition remained unchanged and she was referred and accepted for heart-lung transplantation. Immunosuppressive treatment was not used.[1] In the months that followed a retinal vein thrombosis with secondary glaucoma developed and warfarin treatment was started. She continued to be hypotensive with low output failure, raised venous pressure, and tricuspid regurgitation and was unable to do any housework or look after her child. She was seen frequently in the clinic and it was not until a year after the birth that she began to improve. This improvement was confirmed by serial chest *x* ray (fig 1) and echocardiography (fig 2). Over the course of

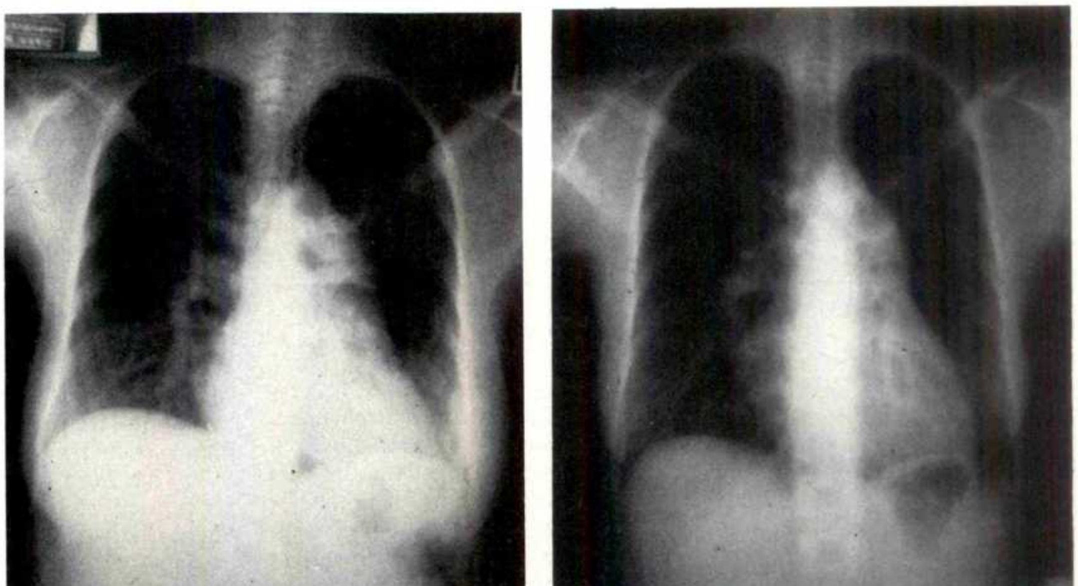

Figure 1 Chest radiographs taken when she was first seen during pregnancy (A), after onset of heart failure (B), and after recovery (C). A and C show an only slightly enlarged heart with evidence of severe pulmonary hypertension but little evidence of left to right shunt. B shows gross cardiomegaly.

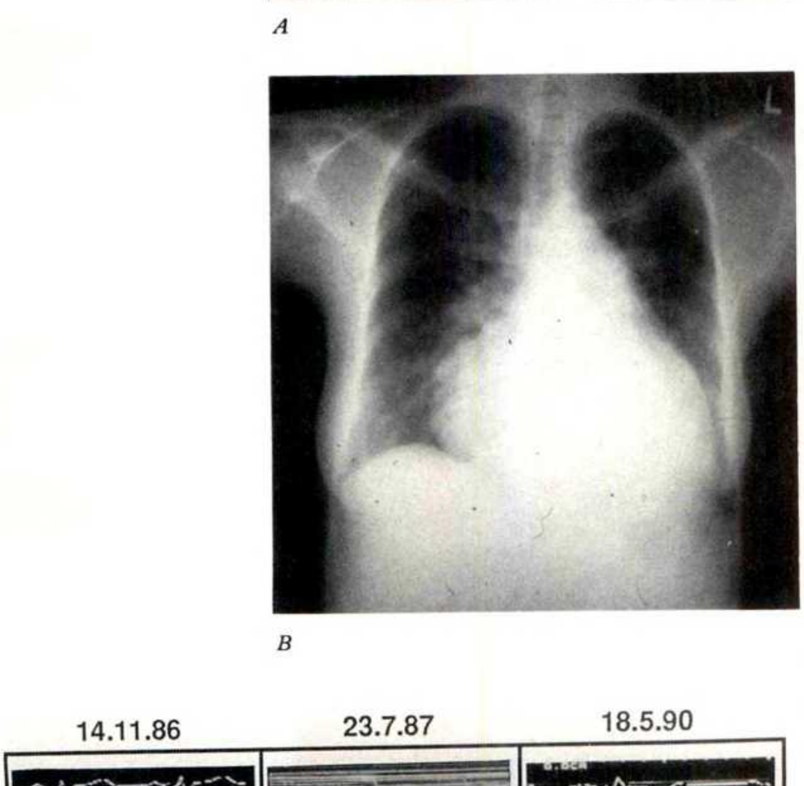

Figure 2 Serial M mode echocardiographic recordings showing good left and right ventricular function on 14 November 1986 but greatly reduced biventricular function on 23 July 1987 with some dilatation. The record of 18 May 1990 showed that ventricular function had recovered. The hypertrophied right ventricle is best seen in the first two records. LV, left ventricular end diastolic (d) and end systolic (s) dimensions; FS, fractional shortening.

more than a further year her left and right ventricular size and function returned to their former state, she is again acyanotic and active with only mild dyspnoea and looking after her family and helping at the playschool to which she takes her daughter. She has been taken off the waiting list for heart-lung transplantation.

Discussion

This 31 year old woman was found to have a ventricular septal defect with a near-Eisenmenger's syndrome during pregnancy. She continued the pregnancy and did well. Three months after delivery profound congestive heart failure developed and she became cyanotic. Heart failure is not a feature of an Eisenmenger ventricular septal defect because the right ventricle has grown and developed at systemic pressure and any potential rise in its systolic or diastolic pressure is immediately dissipated by shunting across the large ventricular septal defect. Myocardial failure is therefore not part of the course. Consequently, we believe that in our patient deterioration in biventricular function was caused by the development of a peripartum cardiomyopathy and was not associated with the ventricular septal defect and pulmonary hypertension.

Peripartum cardiomyopathy was first described by Ritchie in 1849.[2] The diagnosis is made when heart failure develops in the last month of pregnancy or in the first five postnatal months in the absence of a confirmed aetiology or of demonstrable heart disease before the last month of pregnancy.[3 4] The aetiology is unclear but it is probably immunological. Biopsy specimens taken early in the course of the disease have sometimes shown inflammatory changes suggesting a viral or autoimmune mechanism.[1 3 5] Poor nutrition has been suggested[3] though most women affected are well nourished. Pre-eclampsia was seen in a disproportionate number of pregnancies,[3] and the very high incidence of heart failure in pregnant

Data from cardiac catheterisation after onset of heart failure

Data	*Pressures (mm Hg)*		*O$_2$ sat (%)*	*After O$_2$*
Right atrium	20		41	55
Right ventricle	120/24		57	67
Pulmonary artery	110/55	86	53–62	64
Aorta	110/70	90	76·75	89
Q̇P:Q̇S			0·76:1	1·17:1

Q̇P:Q̇S = pulmonary:stystemic flow ratio.

women in parts of Nigeria related to a diet very high in sodium[6] suggests another mechanism. Demakis and Rahimtoola reported that in 82% of patients symptoms developed in the first three postpartum months and in 7% in the last month of pregnancy.[4] Forty eight per cent were over 30 years old and 71% of patients were in their third or subsequent pregnancies. Seven per cent of cases involved twin pregnancies (seven times the expected rate). Some claim that the prognosis is very poor if the heart has not returned to its normal size six months after the diagnosis;[7] but this has not been our experience. As our case shows, recovery may start later and take as long as two years. The outlook for subsequent pregnancies depends on whether the heart returned to normal after the first episode;[7] the condition does not always recur in subsequent pregnancies if recovery has been complete.

Our patient was unusual in having coincidental severe congenital heart disease to which the heart failure could not be attributed. She was also unusual in remaining in heart failure (New York Heart Association Class III–IV) for a year postpartum before she started to improve and then recovering her pre-pregnancy cardiovascular status in the subsequent year. The development of central cyanosis after the onset of heart failure can be explained by a greater admixture of venous blood during the period of low output failure. If cyanosis had been caused only by an increase in pulmonary vascular resistance associated with the pregnancy then, as in the natural history of an Eisenmenger ventricular septal defect, she would have gone blue but not into heart failure, nor would recovery of her former state have been expected.

She has been advised against further pregnancies and sterilisation has been performed. She may still need heart/lung transplantation if progressive pulmonary vascular disease develops.

1 Midei MG, DeMent SH, Feldman AM, *et al.* Peripartum myocarditis and cardiomyopathy. *Circulation* 1990; 81:922–8.

2 Ritchie C. Clinical contributions to the pathology, diagnosis and treatment of certain chronic disease of the heart. *Edinburgh Med Surg J* 1849;12:333.

3 Walsh J, Burch G, Black W, Ferrons V, Hibbs R. Idiopathic myocardiopathy of the puerperium. *Circulation* 1965; 32:19–31.

4 Demakis J, Rahimtoola S. Peripartum cardiomyopathy. *Circulation* 1971;44:964–8.

5 Melvin KR, Richardson P, Olsen E, Daly K, Jackson G. Peripartum cardiomyopathy due to myocarditis. *N Engl J Med* 1982;307:731–4.

6 Seftel H, Susser M. Maternity and myocardial failure in African women. *Br Heart J* 1961;23:43–52.

7 Demakis J, Shahbuden H, Rahimtoola S, *et al.* Natural course of peripartum cardiomyopathy. *Circulation* 1971;44:1053–61.

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MEASUREMENT

Continuity equation and Gorlin formula compared with directly observed orifice area in native and prosthetic aortic valves

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Abstract

Orifice areas calculated by the continuity and Gorlin equations have been shown to correlate well in vivo. The continuity equation, however, gives underestimates compared with the Gorlin formula and it is not clear which is the more accurate. Both equations have therefore been tested against maximal orifice area measured by planimetry in eight prepared native aortic valves and four bioprostheses. A computer controlled, ventricular flow simulator (cycled at 70 beats/min) was used at five different stroke volumes that gave cardiac outputs of 2·8 to 7·0 l/min. The mean difference between measured and estimated orifice area was zero for the continuity equation, but −0·14 cm^2 for the convential Gorlin formula. Thus the Gorlin formula tended to give overestimates compared with both measured area and area estimated by the continuity equation, probably because of the effect of pressure recovery. When predictive equations derived from these data were tested, residual standard deviations were around 0·3 cm^2 at all stroke volumes for the continuity equation, around 0·2 cm^2 for the invasive Gorlin formula, and between 0·2 and 0·4 cm^2 for the modified Gorlin formula. These results suggest that estimates of orifice area in an individual valve as judged by any of the equations tested should be seen as a guide to rather than as a precise measure of actual orific area.

Pressure drop across an aortic valve depends on both transaortic flow and orifice area and is not on its own an adequate measure of stenosis. A better assessment of valve function can be obtained with flow-corrected estimated orifice area as found by, for example, the Gorlin formula.[1,2] Recent work, however, has explored the application of the continuity equation, which is more suited to non-invasive studies.[3-5] The continuity equation assumes that volume flow on either side of an obstruction is the same. A change in flow affects both sides equally so that the ratio of the two is independent of flow. For the aortic valve, effective orifice area can be calculated as the product of subaortic to aortic flow velocity.[6-8] Though good correlations have been shown between orifice area estimates by the continuity equation and the Gorlin formula, results from the continuity equation are usually lower.[3,9,10] It is not known which equation is limited or whether both are.

We have therefore tested both the continuity equation and the Gorlin formula in native and bioprosthetic aortic valves mounted in a flow simulator, with directly observed orifice area as an independent standard.

Methods

VALVES

Eight native valves and four prostheses were tested. The latter comprised two unimplanted Mitroflow bovine pericardial prostheses (Mitral Medical, Canada), annulus diameters 23 mm and 25 mm, and two explanted Carpentier-Edwards prostheses (American Edwards Laboratories, Baxter Healthcare, Santa Ana, CA, USA), diameter 23 mm. One Carpentier-Edwards prosthesis had been clinically normal (CE1) and the other was mildly stenotic and regurgitant (CE2).Two of the native valves were significantly stenotic, one bicuspid (explant 6), and the other tricuspid (explant 7). Two native valves were mildly stenotic (explants 3 and 8) and the other four were normal. The explanted native valves were excised attached to a cuff of aorta 3–5 cm long within six hours of death. All valves were stored at 4°C for one to eight weeks in a preservative solution containing fungicide and antibiotics. The explanted native valves were sewn on to a Teflon ring covered with brushed polyester and the aortic root was supported externally by aluminium stents fixed to each coronary sinus with epoxy resin (fig 1). After tests the valves were radiographed and the degree of calcification estimated semiquantitatively (table 1).[11]

APPARATUS

A positive displacement ventricular flow simulator controlled by computer was used. This was similar to the system described in detail elsewhere,[12] but was modified by the

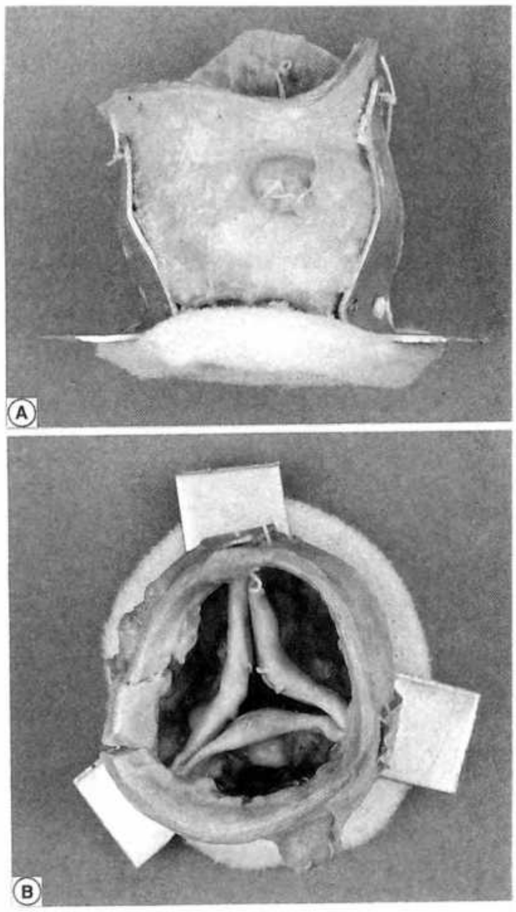


Figure 1 Preparation of an explanted aortic root and valve. The stenotic tricuspid native aortic valve (explant 7) is shown in profile (A) and front view (B). A mounting ring covered with teflon fabric has been sewn to the base of the aortic valve and three shaped aluminium stents fixed to the outside of the coronary sinuses with epoxy resins and a single stitch at the top of each stent.

Table 1 Degree of calcification and subaortic area

	Degree of calcification	*Subaortic area (cm^2)*
Native valves explant:		
1	0	3·8
2	0	3·5
3	+	4·2
4	0	4·5
5	0	2·8
6	++++	3·4
7	+++	6·2
8	++	4·2
Prosthetic valves:		
CE1	0	4·5
CE2	+	4·5
Mitroflow 23 mm	0	4·5
Mitroflow 25 mm	0	4·5

addition of an electromagnetic flowmeter placed 290 mm downstream from the sewing ring and by a removable aortic root (fig 2) which allowed easy insertion of the aortic valves. A copper tubular holder with an ultrasound pencil probe was inserted into a port in the end of the aortic section.

The system was filled with 12 l of normal saline seeded with 5 ml Sephadex. We used quasiphysiological drive waveform to give Doppler waveforms similar to those obtained in vivo (fig 3). A cycle rate of 70 beats/min and stroke volumes of 40, 55, 70, 85, and 100 ml were set with a constant systolic ejection time of 280 ms to give cardiac outputs of 2·8–7·0 l/min (mean transaortic flow 167–417 ml/s). For the first four native valves only stroke volumes of 40, 70, and 100 ml were used. The extra stroke volumes were included in subsequent tests to increase the number of data points. Transaortic flow was measured with an aortic electromagnetic flowmeter and pressure drop by strain gauge pressure transducers (Type 3EA Gaeltec, Dunvegan, Isle of Skye, UK) positioned 25 mm upstream and 100 mm downstream from the aortic prosthesis. Opening of the cusp was recorded by a video camera positioned perpendicularly to the plane of the valve. Strong foreground lighting maximised the contrast. Pressure drop, electromagnetic flowmeter measurements, continuous wave Doppler measurements, and video recordings of valve opening were made simultaneously before a second Doppler probe was inserted for separate recording of subvalvar velocity.

Doppler recordings were made with a Vingmed SD 50 Doppler system (Vingmed, Oslo, Norway). Aortic flow immediately distal to the valve orifice was recorded with continuous wave Doppler from an angled 1·9 MHz Pedof probe. This was held at an angle of about 20° to the long axis of the aorta and then adjusted until the optimal signal was obtained (fig 2). An angle correction was not applied to the aortic velocity measurements. This introduced an underestimation in velocity of about 6% (cos 20°). Subaortic flow was recorded by a 5 MHz in line probe. The tip of the probe was positioned in the centre of the artificial aortic section 3 cm downstream from the valve cusps in their closed position and protruded 2 cm beyond the end of the tubular holder (fig 2). We recorded subaortic flow by pulsed mode with the sample volume set at minimum length and placed within the ventricular chamber 1·0 cm from the mid-plane of the valve mounting ring.

THEORETICAL ASSUMPTIONS

If waveform configuration is assumed to be similar in the aorta and left ventricular outflow tract, the continuity equation based on the law of conservation of mass can be written:

$$A_2 = A_1 \times v_1/v_2 \qquad \text{(equation 1)}$$

where A_1 is subaortic cross sectional area and A_2 maximal aortic orifice area in cm^2, v_1 is peak subaortic velocity, and v_2 is peak aortic velocity in m/s.

The Gorlin formula for invasive use is[1,2]:

$$A_2 = Q/(44{\cdot}3 \times m\Delta P^{\frac{1}{2}}) \text{ (equation 2)}$$

where Q is mean transaortic flow in ml/s and mΔP is the mean pressure drop in mm Hg. The correction constant, 44·3, may not be universally applicable so the formula was generalised to the expression:

$$A_2 \alpha Q/m\Delta P^{\frac{1}{2}} \qquad \text{(equation 3)}$$

In previous in vitro experiments with mitral bioprostheses, we showed an improvement in the correlation between measured and estimated orifice area when peak transvalvar velocity recorded by Doppler ultrasound was substituted for root mean pressure drop.[12]

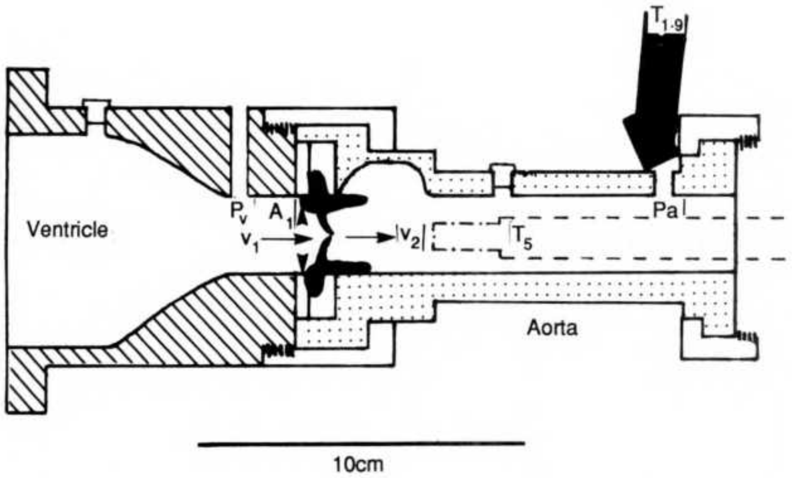


Figure 2 Diagram of the ventricular outflow region and aortic root of the Sheffield flow simulator. From the continuity equation, estimated aortic valve orifice area $= A_1 \times v_1/v_2$. A_1, *subaortic cross sectional area* (cm^2); P_a, *site of aortic pressure measurement;* P_v, *site of ventricular pressure measurement;* $T_{1\cdot 9}$, *Pedof 1·9 MHz angled probe to record aortic flow* T_5, *5 MHz pencil probe within a copper holder to record subaortic flow at the point of measurement of the subaortic area;* v_1, *subaortic velocity (m/s);* v_2, *aortic velocity (m/s).*

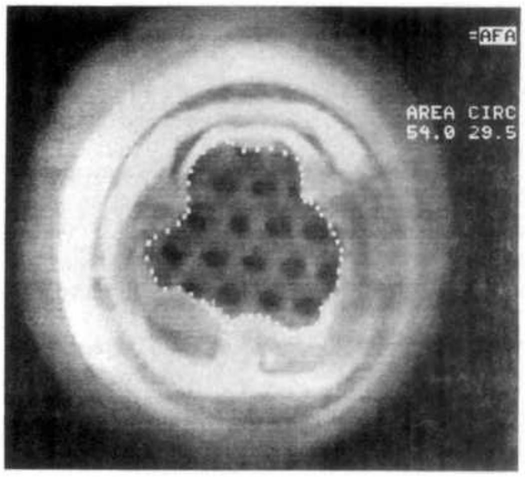


Figure 4 Maximal orifice in a Carpentier-Edwards aortic prosthesis. The frame was recorded at stroke volume 70 ml, cycle rate 70 beats/min in the valve CE1. The white dots are points used to measure directly observed orifice area from a digitised video image by means of the online software of an ultrasound system (Hewlett-Packard 77020A).

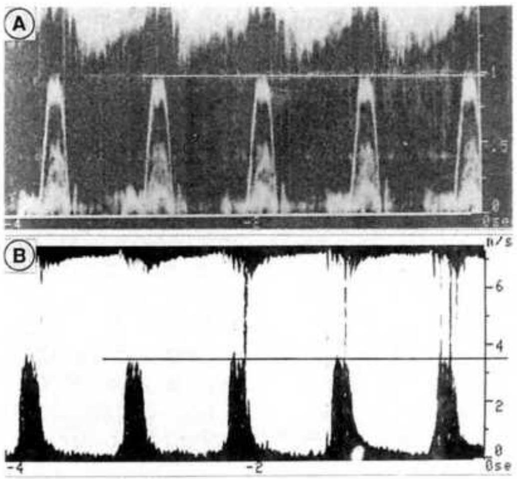


Figure 3 Ultrasound recordings. Both recordings were made at stroke volume 70 ml, cycle rate 70 beats/min in the Carpentier-Edwards bioprosthesis (CE1). Figure 3A shows subaortic velocity recorded with a 5 MHz pencil probe in pulsed Doppler mode with the sample volume set at 1 cm below the cusps in their closed position. Figure 3B shows aortic velocity recorded with a 1·9 MHz Pedof probe. Peak velocity was taken, as shown, from the best fit line through four complexes.

Therefore, in the present study, we also tested a similar modification:

$$A_2 \alpha Q/Vmax \qquad \text{(equation 4)}$$

where V max is peak transaortic velocity in m/s.

DATA ANALYSIS AND STATISTICS

The ultrasound signals were analysed manually and peak transaortic and subaortic velocities taken from the line of best fit through four cycles (fig 3). Transaortic flow was measured every five ms by electromagnetic flowmeter and mean systolic flow was calculated. The video tape of cusp opening was monitored on an echocardiographic system (Hewlett Packard 77020A) and maximum orifice area was measured by planimetry using online analysis software (fig 4). The coefficients of variation for measurements of orifice area were calculated over 54 cycles at seven (13%) of the data points. They ranged from 0·7 to 6·0% with a median of 1·0%. Orifice measurements were corrected for magnification by a factor calculated from the known area of the valve mounting rings.

In some valves the sewing fabric enroached into the left ventricular outflow tract. Subaortic cross sectional area was, therefore, calculated by planimetry of video recordings of the inflow aspect of the mounted valves. To check the reliability of fluid velocity measurements recorded by Doppler ultrasound, they were compared with the peak pressure drop by means of the simplified Bernoulli relation assuming negligible subaortic velocity[13] (peak pressure drop (mm Hg) α $Vmax^2$ where Vmax is peak transaortic velocity in m/s. The correlation between pressure drop and the square of peak velocity was good ($r = 0{\cdot}96$, SD_{res} 63; $y = 4{\cdot}7 + 3{\cdot}1x$) (fig 5).

Agreement between measured and calculated orifice areas was expressed by calculating the mean and 95% confidence intervals (95% CIs) for the differences between paired values. Because 12 different valves were tested at five different stroke volumes, analysis of variance for repeated measurements was performed with valve and stroke volume as factors. Prediction equations and residual standard deviations (SDs) were calculated for each stroke volume.

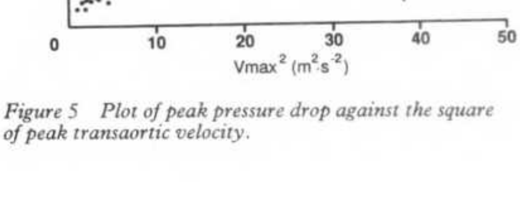


Figure 5 Plot of peak pressure drop against the square of peak transaortic velocity.

Results

CUSP BEHAVIOUR

Measured orifice area was directly related to flow in all valves (fig 6) and the shape of the orifice varied with the type of prosthesis or the aetiology of the aortic stenosis (fig 7). Subaortic velocity was directly related to stroke volume (fig 8).

CONTINUITY EQUATION

The overall mean difference between measured orifice area and area estimated by the continuity equation (equation 1) was 0·00 cm^2. After we allowed for the effect of the 12 different valves, the difference was dependent on stroke volume ($F_{4,36}=8·49$, $p<0·005$). Mean difference at stroke volumes of 40, 55, 70, 85, and 100 ml were −0·13, −0·10, 0·05, −0·01, and 0·16 cm^2 respectively. Thus the continuity equation tended to give underestimates at higher and overestimates at lower stroke volumes.

GORLIN FORMULA

The overall mean difference between measured orifice area and area estimated with the conventional Gorlin formula (equation 2) was −0·14 cm^2. Mean differences at stroke volumes of 40, 55, 70, 85, and 100 ml were 0·04, −0·15, −0·09, −0·18, and −0·33 cm^2. Thus the Gorlin formula tended to overestimate measured orifice area especially at higher stroke volumes.

Figure 6 Plot of maximal orifice area against flow. Data points from all eight native and all four bioprosthetic aortic valves are included.

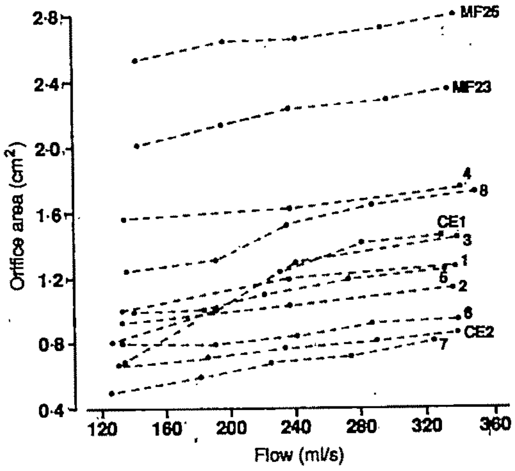
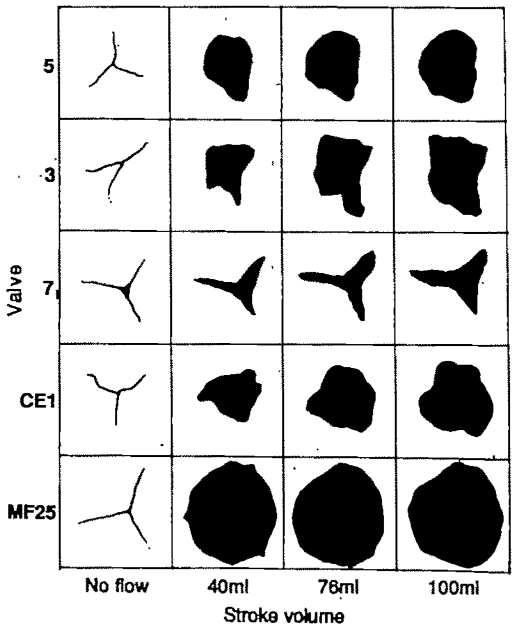


Figure 7 Maximal orifice areas. These were recorded in three native explants (one normal (explant 5), one mildly calcified (explant 3) and one heavily calcified (explant 7)), a Carpentier-Edwards bioprosthesis (CE1), and a Mitroflow bovine pericardial prosthesis (MF 25)). Orifice areas are shown at no flow then at stroke volumes of 40, 70, and 100 ml with a cycle rate of 70 beats/min.



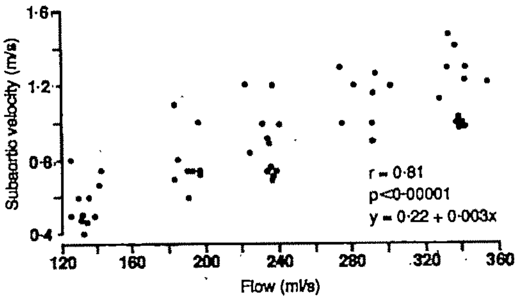


Figure 8 Plot of peak subaortic velocity against mean systolic flow.

EMPIRICAL PREDICTION OF MEASURED ORIFICE AREA

Figures 9 and 10 show plots of measured orifice area against equations 1, 3, and 4. Table 2 gives the prediction equations calculated from these data for each stroke volume. Residual SD was about 0·3 cm^2 for the continuity equation, about 0·2 cm^2 for the invasive Gorlin formula, and between 0·2 and 0·4 cm^2 for the modified Gorlin formula. Figure 11 shows the differences between measured and calculated orifice area compared with stroke volume. The intercepts but not the slopes varied significantly between stroke volumes. When prediction equations were fitted for all stroke volumes combined, the modified Gorlin formula had the smallest residual SD (equation 4).

The empirical invasively based formula derived from our data was:

$$A_2 = Q/(52·6 \times m\Delta P^{\frac{1}{2}}) \text{ (equation 5)}$$

The use of the convential constant, 44·3, would therefore have led to overestimation of orifice area by a factor of 1·18 in all valves considered together. The factor varied between 0·85 and 1·32 when calculated for each valve individually.

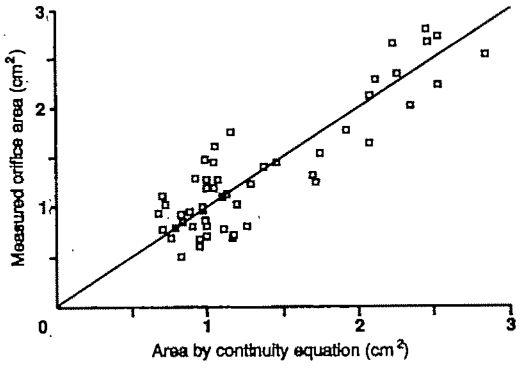


Figure 9 Continuity equation: measured orifice area compared with area estimated by the continuity equation. The line of identity is shown.

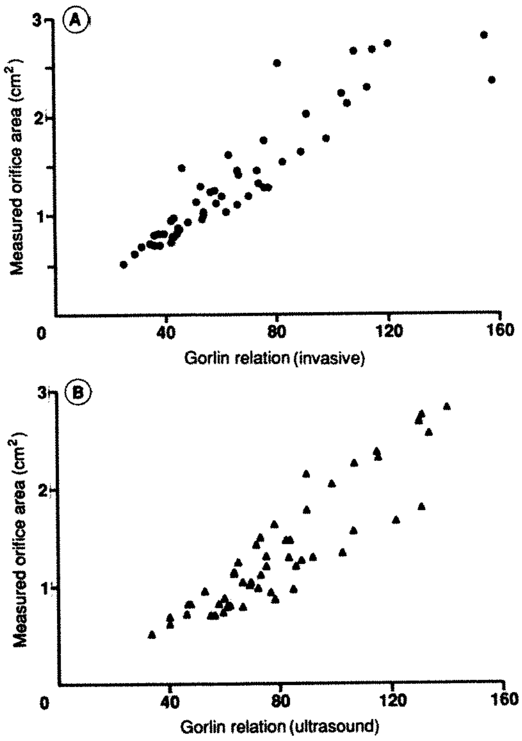


Figure 10 The Gorlin relation. (A) The invasively derived relation (equation 3). (B) The Gorlin relation modified for use with ultrasound (equation 4).

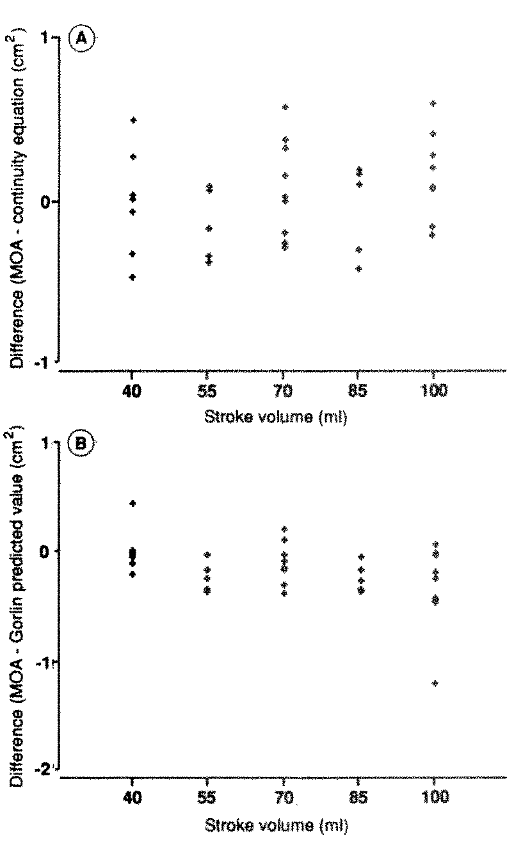


Figure 11 Differences between measured (MOA) and estimated orifice area. Values are grouped by stroke volume for the contuinity equation (A) and invasive Gorlin formula (fig 11B).

Table 2 Comparison of regression lines fitted to predict measured orifice area at different stroke volumes using three equations (residual SD)

Stroke volumes (ml)				
40 (n = 12)	*55 (n = 8)*	*70 (n = 12)*	*85 (n = 8)*	*100 (n = 12)*
		Continuity equation (equation1)		
0·1 + 0·78x (0·29)	−0·4 + 1·2x (0·29)	0·2 + 0·86x (0·29)	− 0·06 + 1·03x (0·25)	0·23 + 0·95x (0·27)
		Invasive Gorlin generalisation (equation 3)		
− 0·3 + 0·03x (0·25)	−0·2 + 0·02x (0·21)	− 0·1 + 0·02x (0·18)	− 0·02 + 0·02x (0·15)	0·3 + 0·02x (0·19)
		Modified Gorlin generalisation (equation 4)		
− 0·4 + 0·02x (0·20)	−0·5 + 0·02x (0·36)	− 0·4 + 0·02x (0·28)	− 0·3 + 0·02x (0·33)	− 0·2 + 0·02x (0·30)

Discussion

Several studies have compared estimates of orifice area by the Gorlin and continuity equations in the clinical situation. These have shown good correlations in routine studies[3 4 7] or before and after balloon dilatation,[9] but the continuity equation has tended to give an underestimate compared with the Gorlin equation. In the present study, the conventional Gorlin formula (equation 2) overestimated orifice area, when compared with measured area, whereas the continuity equation gave a mean difference of zero. Thus in previously published studies it is likely that overestimates were given by the Gorlin formula rather than underestimates by the continuity equation.

SOURCES OF ERROR IN THE GORLIN FORMULA

The most important cause for systematic overestimation of orifice area by the Gorlin formula is likely to have been neglect of pressure recovery. Because fluid loses momentum beyond an orifice, kinetic energy is converted to pressure energy. Static pressure increases and ultimately approaches its prestenotic value, although complete recovery is limited as a result of changes in chamber geometry and because some energy is lost through turbulence.[14] In our system, the pressure transducer was located 100 mm downstream from the annulus of the valves at a point where pressure recovery would have been complete. The situation in clinical practice is similar because a fluid filled catheter must be positioned beyond the point where "whip" artefact makes pressure recordings unreliable. Underestimation of the transaortic pressure drop is accentuated when femoral artery pressure rather than aortic pressure is measured.[10] Other possible sources of error are the difference in density between blood and physiological saline (although by a factor of only 1·05), the use of root mean pressure drop instead of the mean of root pressure drop, and changes in the correction constant at extremes of flow.[14 15]

Our results differ from those of Segal *et al* who showed that the Gorlin formula tended to underestimate compared with the continuity equation.[15] In that study the pressure transducer was placed close to the orifice so that pressure recovery would have been small. Underestimation could have been caused mainly by a fall in discharge coefficient (this implies an increase in pressure drop as a result of viscous friction) at Reynold's numbers below a critical value. This value was shown to be directly related to orifice area and in that experiment areas up to 4·5 cm^2 were used; these were larger than in the present study.

The average overestimation of orifice area calculated from our regression equation was 1·2. Correction factors calculated for individual valves, however, ranged from 0·9 to 1·3. Hence variability in estimated orifice area was increased by the use of an average value. Other workers have also shown that discharge coefficients vary between valves and depend on the geometry and area of the orifice.[15 16] The same problem would affect the accuracy of the Gorlin formula in the clinical situation.

SOURCES OF ERROR IN THE CONTINUITY EQUATION

The continuity equation is not limited by the effect of pressure recovery because velocity can be measured in line with flow, and peak instantaneous velocity can be assumed to have been recorded at the point of maximum pressure drop. Thus in the present study the mean difference between estimated and measured orifice area was zero.

Residual SDs were around 0·3 cm^2, which means that orifice area may be predicted to within 0·6 cm^2 for 95% of individual readings. The equation tended to underestimate at high and overestimate at low stroke volumes. These discrepancies are difficult to explain. The cause of overestimation may have been erroneously low peak transvalvar velocity measurements, although the fact that the relation between peak pressure drop and peak instantaneous velocity did not vary significantly makes this unlikely. Underestimation could theoretically be caused by erroneously low subaortic velocities although these seemed to change consistently with flow in each prosthesis (fig 8). Possibly changes in stroke volume caused differences in convective flow acceleration in the subaortic region,[17] while the position of the pulsed wave sample volume remained fixed.

VALIDITY OF MEASURED ORIFICE AREA

The validity of directly observed orifice area as a reference standard depends on three factors: the accuracy of its calculation, whether maximal area is more appropriate than mean area, and on the relation between hydrodynamic and anatomical orifice area.

There may have been small errors in measurement where the edges of the orifice were irregular. This, however, was only a potential problem in three valves (explants 6 and 8 and CE 2). The image used for planimetry, furthermore, was magnified so that any errors were reduced by a factor of about 40; this made them insignificant.

Effective area calculated by the Gorlin formula uses the square root of mean pressure drop. This is unlikely to have caused major inconsistencies because normal native aortic valves open and close quickly, within approximately 30 ms, and therefore remain at maximum area through most of systole.[16] Also, the use of peak transaortic velocity, which occurs at the same time as maximum orifice area, in the modified Gorlin formula did not improve the correlation with actual orifice area.

Anatomical orifice area measured by planimetry may differ from effective hydrodynamic orifice area in some circumstances. In stenotic valves flow lines continue to converge beyond the orifice as far as the vena contracta. At this point the pressure drop will be greater than at the orifice and the hydrodynamic orifice area will be correspondingly smaller than the measured orifice area. Normally functioning bioprostheses behave as nozzles. They do not develop a vena contracta but have mechanical energy losses that depend on the shape of the nozzle. These increase the transvalvar pressure drop so that, again, effective orifice area is smaller than orifice area measured by planimetry.[18] Thus, in general, effective orifice area is expected to be slightly smaller than measured orifice area although the Gorlin formula contains constants intended to correct for this difference.

Measured orifice area as used in this study is not a perfect reference standard. The errors in its measurement are, however, small and although differences in valve shape and behaviour may have contributed to inconsistencies between anatomical and hydrodynamic orifice area, this effect is not expected to have been large.

LIMITATIONS

In the Sheffield flow simulator, the volume flow rate is constrained but the pressure that can be developed within the ventricle is not limited. The left ventricular outflow tract and aortic root have a shape similar to that of the real heart, but are rigid. Thus although physiological waveforms, peripheral compliance, and peripheral resistance are modelled to first order, the simulator is not a perfect representation of the real heart. The native valves were mounted in a rigid annulus by means of a sewing ring and aluminium stents and their behaviour may have differed in detail from native valves in vivo.

The presence of the ultrasound probe holder should not have introduced errors as it was used solely for recording subaortic velocity. Although its presence may have caused flow acceleration, this would have begun about 6 cm downstream from the point of velocity measurement. Orifice area and peak aortic velocity measurements were made with the holder removed. The angle subtended between the probe and the axis of the aorta would have caused an underestimation of flow velocity and therefore an overestimation of orifice area of about 6%.

Despite the artificial nature of the model, the wide tolerance limits for paired values in this study almost certainly reflect clinical reality. Thus in the study of Oh *et al*, 27% of patients had discrepancies between the continuity equation and Gorlin formula in the diagnosis of aortic valves with effective areas of less than 0·75 cm^2.[7] Standard errors of the estimate for the comparison between the Gorlin formula and continuity equation in published studies range from 0·16 to 0·40.[3 6–9] In the present study standard errors were around 0·01 for comparisons between estimated and measured orifice area.

CLINICAL RELEVANCE

An orifice area estimate has relatively wide CIs so that it should not be used alone in making clinical decisions. Thus Kennedy *et al* studied patients with aortic stenosis, which was defined as moderate solely on the basis of an orifice area estimate of between 0·7 and 1·2 cm^2 from the Gorlin formula.[19] The fact that 82% had symptoms and the four year prognosis was poor suggests that the degree of stenosis may have been underestimated. A balanced judgement about the degree of disease has to be made based on numerous criteria including the clinical assessment, the state of the left ventricle, and the transvalvar velocity as well as the estimated orifice area.

CONCLUSION

In this study, the empirically derived Gorlin constant was higher than the conventional term probably because of the effect of pressure recovery. The regression line of the continuity equation for measured orifice area against estimated orifice area was close to the line of identity. When compared in a population of valves, therefore, the conventional Gorlin formula is expected to overestimate and the continuity equation to be similar to measured orifice area. The 95% CIs of either the empirically derived Gorlin formula or the continuity equation were wide. This suggests that both formulas should be regarded as providing a semiquantitative guide rather than a precise measure of orifice area.

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1 Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J* 1951; 41:1–29.
2 Cohen MV, Gorlin R. Modified orifice equation for the calculation of mitral valve area. *Am Heart J* 1972;84: 839–40.
3 Zoghbi WA, Farmer KL, Soto JG, Nelson JG, Quinones MA. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation* 1986;73:452–9.
4 Teirstein P, Yeager M, Yock P, Popp RL. Doppler echocardiographic measurement of aortic valve area in aortic stenosis: a noninvasive application of the Gorlin formula. *J Am Coll Cardiol* 1986;8:1059–65.
5 Richards KL, Cannon SR, Miller JF, Crawford MH. Calculation of aortic valve area by Doppler echocardiography: a direct application of the continuity equation. *Circulation* 1986;73:964–9.
6 Skjaerpe T, Hegrenaes L, Hatle L. Non-invasive estimation of valve area in patients with aortic stenosis by Doppler ultrasound and two dimensional echocardiography. *Circulation* 1985;72:810–8.
7 Oh JK, Taliercio CP, Holmes DR, Reeder GS, Bailey KR, Seward JB, *et al.* Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol* 1988;11:1227–34.
8 Otto CM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol* 1986;7:509–17.
9 Come PC, Riley MF, McKay RG, Safian R. Echocardiographic assessment of aortic valve area in elderly patients with aortic stenosis and of changes in valve area after percutaneous balloon valvuloplasty. *J Am Coll Cardiol* 1987;10:115–24.
10 Goli VD, Teague SM, Prasad R, Harvey J, Voyles WF, Olson EG, *et al.* Noninvasive evaluation of aortic stenosis severity utilizing Doppler ultrasound and electrical bioimpedance. *J Am Coll Cardiol* 1988;11:66–71.
11 Schoen FJ, Kujovich JL, Webb CL, Levi RJ. Chemically determined mineral content of explanted porcine valve bioprostheses: correlation with radiographic assessment of calcification and clinical data. *Circulation* 1987;76: 1061–6.
12 Chambers JB, Cochrane T, Black MM, Jackson G. The Gorlin formula validated against directly observed orifice area in porcine mitral bioprostheses. *J Am Coll Cardiol* 1989;13:348–53.
13 Stamm RB, Martin PR. Quantitification of pressure gradients across stenotic valves by Doppler ultrasound. *J Am Coll Cardiol* 1983;2:707–18.
14 Tindale WB, Trowbridge EA. Modification of the Gorlin equation for use with heart valve substitutes. *Cardiovasc Res* 1986;20:458–65.
15 Segal J, Lerner DJ, Miller DC, Mitchell RS, Alderman EA. Popp RL. When should Doppler-determined valve area be better than the Gorlin formula?: variation in hydraulic constants in low flow states. *J Am Coll Cardiol* 1987; 9:1294–305.
16 Thubrikar M, Bosher LP, Nolan SP. The mechanism of opening of the aortic valve. *J Thorac Cardiovasc Surg* 1979;77:863–70.
17 Pasipoularides A, Murgo JP, Bird JJ, Craig WE. Fluid dynamics of aortic stenosis: mechanisms for the presence of subvalvular pressure gradients. *Am J Physiol* 1984; 246:H542–50.
18 Clark C. The fluid mechanics of aortic stenosis: I Theory and steady flow experiments. II Unsteady flow experiments. *J Biomech* 1976;9:521–8, 567–73.
19 Kennedy KD, Nishimura RA, Holmes DR, Bailey KR. Natural history of moderate aortic stenosis. *J Am Coll Cardiol* 1991;17:313–9.

BRITISH CARDIOLOGY

Need for invasive cardiological assessment and intervention: a ten year review

C A MacRae, M S Marber, Charlotte Keywood, M Joy

Abstract

The uptake of invasive cardiological investigation and cardiopulmonary bypass procedures by the North West Surrey Health District was audited over the years 1979–88. Growth was almost continuous throughout the ten year period. The need within the district each year for coronary angiography seemed to be between 111 and 171 and for surgical revascularisation of the myocardium between 63 and 96 procedures; the first figure is the mean of the second quinquennial period (1984–88) and the second figure the total for 1988. After correction for the standardised mortality ratio and catchment area, the national requirement should lie between 690 and 1070 coronary angiograms and 390 and 600 coronary artery bypass graft operations per million population each year. There is a further national requirement for 70 valvar heart operations and 30 miscellaneous procedures per million population each year. Owing to delays in the provision of services, 20 patients died of a cardiovascular cause while they were on the waiting list for investigation or surgery. In the United Kingdom the annual target to be achieved by 1990 was 300 coronary artery bypass procedures per million population.

There is a widely held consensus about the need for information in the medical specialities upon which to base planning for health care provision, but there are few objective data available. In cardiology this is despite well-defined end points.[1] Our unit has previously reported on its uptake of invasive cardiological services and projections were made towards the United Kingdom national requirement.[2] Between 1979 and 1984 a significant increase in uptake of resource was demonstrated, a trend that has continued. This report, while containing some of the earlier data, relates to the substantially expanded data base which now covers the years 1979 to 1988 inclusive.

Patients and methods

St Peter's Hospital, Chertsey, is the district hospital serving the North West Surrey Health District (South West Thames Regional Health Authority). The mean population of the district during the ten year study period was 205 000; there was a skew in social distribution towards classes I and II, and a younger than average age distribution. The standardised mortality ratio for ischaemic heart disease (ICD 410–414) for the district was 0·78 and for valvar heart disease (ICD 393–398) it was 1·0.[3]

Patients from the health district (whether within the National Health Service or the private sector) requiring invasive cardiological assessment or investigation or both are referred by the district cardiological unit. Two audits (1983, 1986)[2] indicated that referral of "in district" patients made by other means was closely matched by cross boundary inflow of patients from without the district. Information on demography, symptoms, medication, non-invasive assessment, and the date and outcome of invasive investigation or intervention on patients referred is recorded on an ongoing data base.

"Ischaemic heart disease" in this study includes chronic stable angina, the acute coronary syndromes, atypical chest pain requiring angiography, and heart failure secondary to coronary artery disease with or without non-rheumatic mitral valve regurgitation. "Valvar heart disease" includes isolated aortic valve disease with or without coronary artery disease, chronic rheumatic heart disease affecting at least one heart valve, and mitral leaflet prolapse requiring investigation/surgery. Conditions falling outside these broad categories are grouped together as "other".

Symptoms are classified according to the New York Heart Association criteria.[4] Invasive data are recorded as reported by the investigating cardiologist at the regional cardiac centre, with the severity, number, and site of coronary artery stenoses being noted and classified according to the European trial criteria.[5] The presence or absence of left ventricular impairment at angiography is recorded. All deaths including those of patients on the waiting lists,[6] at operation, or up to 28 days after operation are recorded and the cause established.

The indications for referral for invasive investigation are influenced to some extent by patient age. Over the ten year study period there was a trend to operate on increasingly older patients, which reflects the improved outcome and appreciation of the considerable symptomatic benefit that revascularisation may bring in the older patient.[7] In addition, the initial enthusiasm for surgical intervention

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to improve prognosis was tempered during this period which also saw the emergence of improved pharmacological agents.[8] It is the policy within the unit for all patients with stable angina pectoris to have a symptom limited exercise electrocardiogram unless there is some absolute contraindication.[9] Medical treatment is considered to have failed if patients still have New York Heart Association grade II symptoms of angina while being treated with at least two of the three major groups of pharmacological agents available in adequate dosage.[10] Aspirin was normally given from 1985 onwards.

Patients who need investigation of unstable angina (NYHA grade IV) are referred directly to a regional centre usually after not less than 48 hours of administration of antianginal agents including a β adrenoceptor blocking agent, intravenous nitrates, and heparin or aspirin or both. If patients with a very low threshold for symptoms have electrocardiographic changes on submaximal exercise they may be transferred for invasive investigation. It is departmental policy that after suspected or proven myocardial infarction all patients aged less than 60 have symptom limited exercise electrocardiography. Most patients aged > 60 but < 65 as well as selected older patients with no upper age limit are also investigated unless there is a contraindication.

Results

Figure 1 shows the total number of patients referred by the district unit for invasive investigation and intervention during the period 1979–88. There was a sustained growth in the number of patients referred for investigation of ischaemic heart disease, which was paralleled by the numbers undergoing subsequent coronary artery bypass grafting. The downturn in 1984–85 coincided with a change in main referral centre from St Thomas's Hospital, Lambeth, to St George's Hospital, Tooting.

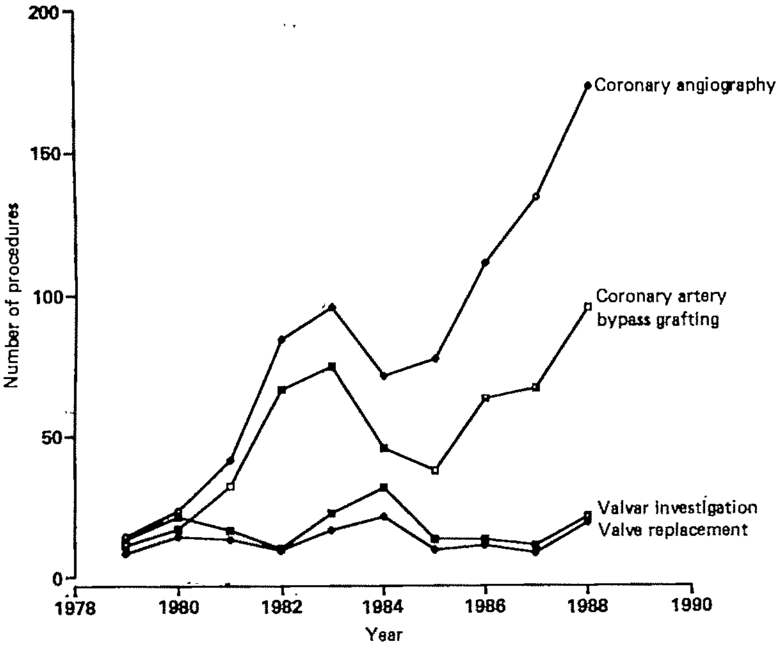

Figure 1 Growth in referral of patients for cardiac catheterisation, coronary angiography, valvar surgery, and coronary artery bypass grafting over the ten years 1979–88.

Of 823 patients referred with suspected ischaemic heart disease, 11 were never investigated (refused, died), 31 were reclassified on account of other cardiac abnormalities (valvar heart disease, transplantation, malignant rhythm disturbance, conducting tissue disease) and of the 781 remaining, 495 (63·4%) subsequently underwent coronary artery bypass grafting and 40 (5·1%) percutaneous transluminal coronary angioplasty. The mean age of patients referred for coronary artery bypass grafting increased during the study period (fig 2). The ratio of males to females fell from approximately 6:1 to 4·5:1 in the second half of the study period. Of patients referred, 15·9% had unstable symptoms and this included patients referred for routine investigation in whom symptoms subsequently became unstable. Symptoms were still significant in over three quarters of all patients (NYHA grade I, 16%; grade II/III, 68%; grade IV, 16%) despite treatment. Previous myocardial infarction had been documented in 46% of all patients and 49% were shown to have an abnormal left ventriculogram.

Six patients died while they were on the waiting list for angiography (table 1). All had NYHA grade II/III angina. There were nine cardiac deaths in patients on the waiting list for bypass grafting (table 2). All but one were known to have both triple vessel disease and impaired left ventricular function. These figures do not include two deaths that occurred within 24 hours of angiography or four non-cardiac deaths. The distribution of coronary disease according to the European Coronary Surgery study critera[5] was: nil significant, 30; single vessel, 163; two vessel, 206; three vessel, 355; and left main stem, 27. The operative mortality for coronary artery surgery fell from 6·5% in the first five years to 2·0% in the second five years.

The mean age of patients undergoing surgery for valvar heart disease rose slightly during the study period to 64·6 years. There was no

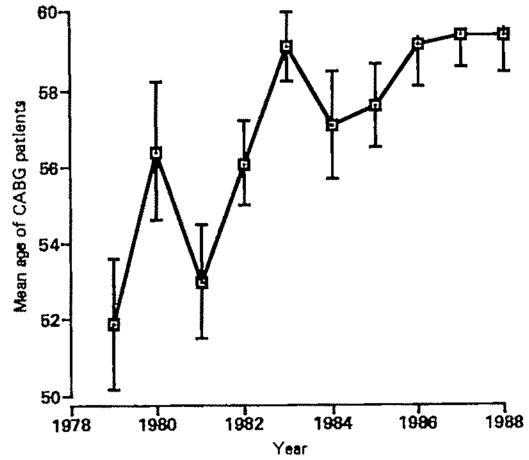

Figure 2 Mean (SEM) age of patients undergoing surgery during the years 1979–88.

Table 1 Length of time on waiting list (WL) for investigation and severity of angina in those who died while on the waiting list

Case	*Time (days) on WL*	*NYHA grade*
1	28	III
2	30	III
3	56	III
4	63	III
5	120	II
6	180	II

Table 2 Length of time on waiting list (WL) for surgery and severity of disease in those who died while on the waiting list

Case	*Time (days) on WL*	*Disease extent*	
1	28	3VD	Impaired LV
2	29	2VD	Normal LV
3	50	3VD	Impaired LV
4	55	3VD	Impaired LV
5	160	3VD	Impaired LV
6	208	3VD	Impaired LV
7	260	3VD	Impaired LV
8	291	3VD	Impaired LV
9	400	3VD	Impaired LV

3VD, three vessel disease; LV, left ventricle.

difference in representation of the sexes. Of 177 patients referred for investigation, 139 (78·5%) subsequently underwent surgery. Aortic valve disease was present in 88 patients (49·7%) and 15 of these had coexistent coronary artery disease requiring grafting. The overall operative mortality for valvar surgery was 4·3%. There was one death among patients on the waiting list for investigation. Two patients, both with severe aortic stenosis, died within 24 hours of cardiac catheterisation and there were three cardiac deaths on the surgical waiting list.

Of 184 permanent pacemaker units implanted, 94·6% were ventricular demand systems. The waiting time to unit implantation for symptomatic complete atrioventricular block rose from a mean (SEM) of 2·6 (0·5) days in 1982 to 47·5 (12·0) days in 1988. One patient on the waiting list for permanent pacing died.

Table 3 shows the patients referred for miscellaneous procedures. The numbers in each category are too small for further analysis.

Discussion

There is a consensus on the assessment of prognosis of ischaemic heart disease,[11] on the role of invasive investigation,[12] and on the part played by revascularisation of the myocardium and its management.[13 14] Symptoms of angina that do not respond to medical treatment and a high risk of myocardial ischaemic events demand angiography. Surgical revascularisation may improve both the symptoms and the prognosis in certain patterns of disease,[11] although the benefits of surgery may not be long lasting.[14] A sixth of all our referred patients had unstable angina, and a further two thirds had grade II/III symptoms while receiving treatment. Left main stem and three or two vessel coronary artery disease was present in three quarters of all patients investigated.

There was an almost continuous growth in the uptake of invasive cardiological services over the ten year period 1979–88 in North West Surrey, which has shown no sign of abating. The downturn in patient referral in 1984–85 that coincided with the change in referral centre reflected to some extent re-evaluation of the benefits of surgical intervention in terms of prognosis. In the five years 1984–88 the mean (SEM) number of patients referred for coronary angiography and surgical revascularisation of the myocardium was 110·0 (22·7) and 62·8 (13·6) respectively. After adjustment for the catchment population, this represents a mean of 540 and 306 procedures per million population a year respectively. In 1988 the district uptake was 171 coronary angiographic and 96 coronary artery bypass procedures (830 and 470 respectively per million population a year). In sharp contrast valvar investigation and intervention remained constant throughout the ten year period, with a mean annual requirement for 18 investigations and 14 valvar operations (88 and 70 per million population) respectively.

But North West Surrey has a lower than average death rate from coronary heart disease.[3] By taking into account the standardised mortality ratios for the health district for ischaemic heart disease (0·78) and for valvar heart disease (1·0), we projected the national need by dividing the district population requirement by the mortality ratios. Based on our experience, therefore, there appears to be a national annual requirement for at least 690 coronary angiographic procedures and 390 coronary artery bypass procedures per million population, the valvar figure remaining unmodified. Because the numbers are tending to rise, this is likely to be an underestimate. If one were to rely on the 1988 experience alone, then the relevant figures would be 1070 coronary angiographic procedures and 600 coronary artery bypass procedures per million population per annum. The number of patients undergoing percutaneous transluminal angioplasty was too small for such analysis.

In the United Kingdom, in 1986 the

Table 3 Miscellaneous procedures in patients referred to the regional cardiac centre 1979–88

Procedure	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*	*Total*
EPS	5	1	2	0	3	2	0	5	5	2	25
Cardiomyopathy	1	4	0	1	2	3	1	2	2	1	17
Transplant	0	0	0	0	0	0	0	1	0	4	5
Congenital	4	1	0	4	0	1	1	0	1	1	13
Aortic dissection	1	1	1	2	0	0	1	0	0	1	7
Pulmonary embolism	0	0	3	0	0	1	0	0	0	0	4
Pericardial	0	0	2	1	1	1	0	1	1	0	7
Permanent pacing	5	15	8	21	18	13	18	32	22	35	187
Total	16	22	16	29	24	21	21	41	31	44	265

EPS, electrophysiological study.

Secretary of State announced an annual target of 300 coronary artery bypass graft operations per million population in England by 1990 from within planned resources.[1] This target compares unfavourably with Australia (600) and the United States of America (1000),[1] where the incidence of coronary artery disease is roughly similar. We have previously commented that this target[2] appears to be a serious underestimate unless our experience is unrepresentative and this seems unlikely from our analysis of the pattern of disease encountered. The demonstrated shortfall in available care has consequences in economic terms and in terms of morbidity and of mortality for those patients who are not privately insured. In the North West Surrey Health District there appears to be a two tier system with unacceptable and increasing delays in the public sector.[6] This may be attributed to inadequate provision related to funding in this sector.

Resources are finite but it is to be hoped that the demonstrated need will permit fairer and more objective decision making in terms of health care policy.[15]

1 National Audit Office. *National Health Service: coronary heart disease*. London: HMSO, 1989.
2 Cripps T, Dennis MS, Joy M. The need for invasive cardiological assessment and operation: viewpoint of a district general hospital. *Br Heart J* 1986;**55**:488–93.
3 Office of Population Censuses and Surveys. *Mortality statistics: cause*. London: HMSO, 1987.
4 Criteria Committee, New York Heart Association. *Diseases of heart and blood vessels. Nomenclature and criteria for diagnosis*. 6th ed. New York: Little Brown, 1964.
5 European Coronary Surgery Study Group. Longterm bypass results of prospective randomised study of coronary artery surgery in stable angina pectoris. *Lancet* 1982; **ii**:1173–80.
6 Marber M, MacRae CA, Joy M. Delay to invasive investigation and revascularisation for coronary heart disease in South West Thames Region. A two tier system? *BMJ* 1991;**302**:1189–91.
7 Loop FD, Lytle BW, Cosgrove DM, *et al*. Coronary artery bypass graft surgery in the elderly. Indications and outcome. *Cleve Clin J Med* 1988;**55**:23–4.
8 Califf RM, Havell FE, Lee KL, *et al*. The evolution of medical and surgical therapy for coronary artery disease. A fifteen year perspective. *JAMA* 1989;**261**:2071–86.
9 Bonow RO, Kent KM, Rosing DR, *et al*. Exercise-induced ischemia in mildly symptomatic patients with coronary artery disease and preserved left ventricular function. Identification at risk of death during medical therapy. *N Engl J Med* 1984;**311**:1339–45.
10 Tobins M, Weir EK, Chester E, *et al*. "Maximal" drug therapy is not necessarily optimal in chronic angina pectoris. *J Am Coll Cardiol* 1984;**3**:1051–8.
11 Rutherford JE, Braunwald E. The selection of patients for the surgical treatment of coronary artery disease. *Q J Med* 1988;**67**:369–85.
12 Goldschlager N, Seltzer A, Conn K. Treadmill tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* 1976;**85**:277–86.
13 Coronary Artery Surgery Study (CASS). A randomised trial of coronary artery bypass surgery. *Circulation* 1983; **68**:939–50.
14 Varnauskas E. European Coronary Study Group. Twelve year follow up of survival in the randomised European Coronary Surgery Study. *N Engl J Med* 1988;**319**:332–7.
15 *Working for patients. Medical audit: working paper 6*. London: HMSO, 1989.

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Balloon dilatation of supravalvar pulmonary stenosis after arterial switch procedure for complete transposition

Sir,—I read with interest the article by Saxena *et al* on balloon dilatation of supravalvar pulmonary stenosis that developed after previous anatomical correction of transposition of the great arteries.[1] They described the results of eight balloon dilatations in five children. In none of the dilatations was there any improvement in the pressure gradient across the area of obstruction nor was there any significant angiographic change. Yet they went on to apply balloon angioplasty in five patients and in addition repeated the procedure in three children. As they state, the residual obstruction seems to be related to shrinkage and retraction of the pericardial patch used in the enlargement of neopulmonary artery at the time of initial surgery. There is no theoretical basis why such lesions would respond to balloon dilatation. Zeevi *et al's* observations were also similar when there was diffuse narrowing of the pulmonary artery.[2] I have also used balloon dilatation of supravalvar pulmonary stenosis that developed after a previous arterial switch procedure.[3] There was excellent haemodynamic (fig 1) and angiographic (fig 2) improvement; however, the obstruction in my case was discrete (fig 1A) and there is theoretical reason for balloon dilatation to be effective discrete obstructions such as this.

I urge Saxena *et al* and others not to use balloon angioplasty if obstructive lesions of the pulmonary artery in children are diffuse, those described by Saxena and Zeevi.[1] Discrete lesions, however, can be dilated.

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1 Saxena A, Fong LV, Ogilvie BC, Keeton BR. Use of balloon dilatation to treat supravalvar pulmonary stenosis developing after anatomic correction for complete transposition. *Br Heart J* 1990;**64**:151–5.
2 Zeevi B, Keane JF, Perry SB, Lock JE. Balloon dilatation of postoperative right ventricular outflow obstructions. *J Am Coll Cardiol* 1989;**14**:401–8.
3 Rao PS. Balloon angioplasty and valvuloplasty in infants, children and adolescents. *Curr Probl Cardiol* 1989;**14**:417–500.

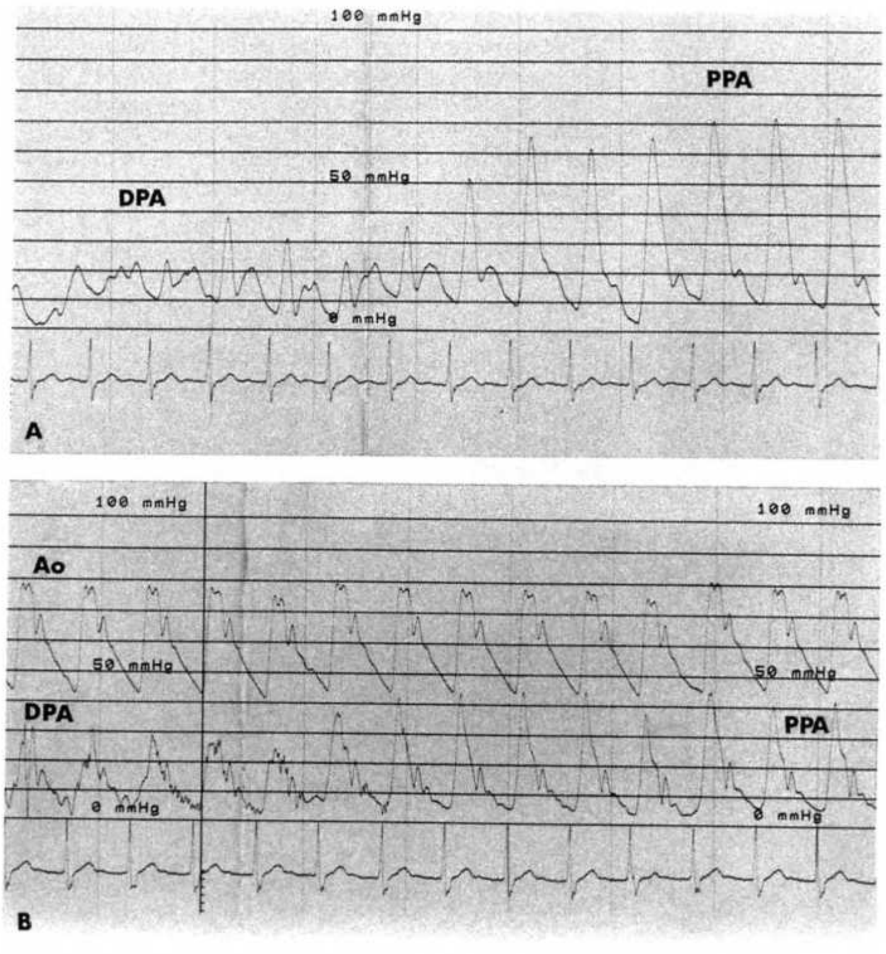

*Figure 1 Pressure pullback tracings across the supravalvar stenosis showing a significant pressure gradient (A) that diminished considerably after balloon dilatation (B). Aortic pressure is also shown in B. Ao, aorta; DPA, distal pulmonary artery; PPA,. proximal pulmonary artery. Reproduced with permission from the author and publisher: Rao PS. Curr Probl Cardiol 1989;**14**:417–500.*

This letter was shown to the authors, who reply as follows:

Sir,—Dr Rao has misinterpreted the nature of the stenotic lesions of the supravalvar pulmonary area that we attempted to dilate after the arterial switch procedure. The angiographic appearances of the cases,[1] showed a stenotic segment that seemed to be localised to a short segment in the proximal pulmonary artery which was considerably narrower than the distal pulmonary arterial segment. The distal pulmonary artery may have looked smaller than expected, but it was comparable to the more distal pulmonary arterial tree, except where a further localised stenosis occurred. It was this short segment of proximal supravalvar pulmonary stenosis or discrete bifurcation stenosis that responded poorly to balloon dilatation. The segments appeared amenable to balloon dilatation, as judged by angiography, and did not assume the appearance of diffuse narrowing that Dr Rao has described. It was concluded that these short localised segments that responded poorly to balloon dilatation should not be described as a discrete stenosis, as their appearance suggested, because they responded like short segments with hypoplasia with both an intrinsic and post-surgical aetiology. We agree with Dr Rao that diffuse hypoplasia would not be amenable to balloon dilatation. Progress in developing effective treatment for such stenotic lesions comes not only from knowledge of successful trials, but also from unsuccessful attempts, as anticipated by the use of endovascular stents for congenital heart disease.[2]

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1 Saxena A, Fong LV, Ogilvie BC, Keeton BR. Use of balloon dilatation to treat supravalvar pulmonary stenosis developing after anatomical correction for complete transposition. *Br Heart J* 1990;**64**:151–5.
2 O'Laughlin MP, Perry SB, Lock JE, Mullins CE. Use of endovascular stents in congenital heart disease. *Circulation* 1991;**83**:1923–39.

Balloon atrial septostomy via the umbilical vein

Sir,—We wish to point out that the "practicability of cannulation via the umbilical vein"[1] was first reported by us as an alternative to the femoral route for balloon atrial septostomy over two decades ago.[2] Several centres have adopted the method and have confirmed the usefulness and advantages of this approach.[3-5] One report was published in the *British Heart Journal* in 1974[6] with similar conclusions to ours. The incorporation of echocardiographic imaging makes the umbilical route even more attractive. We highlighted the fact that transumbilical sep-

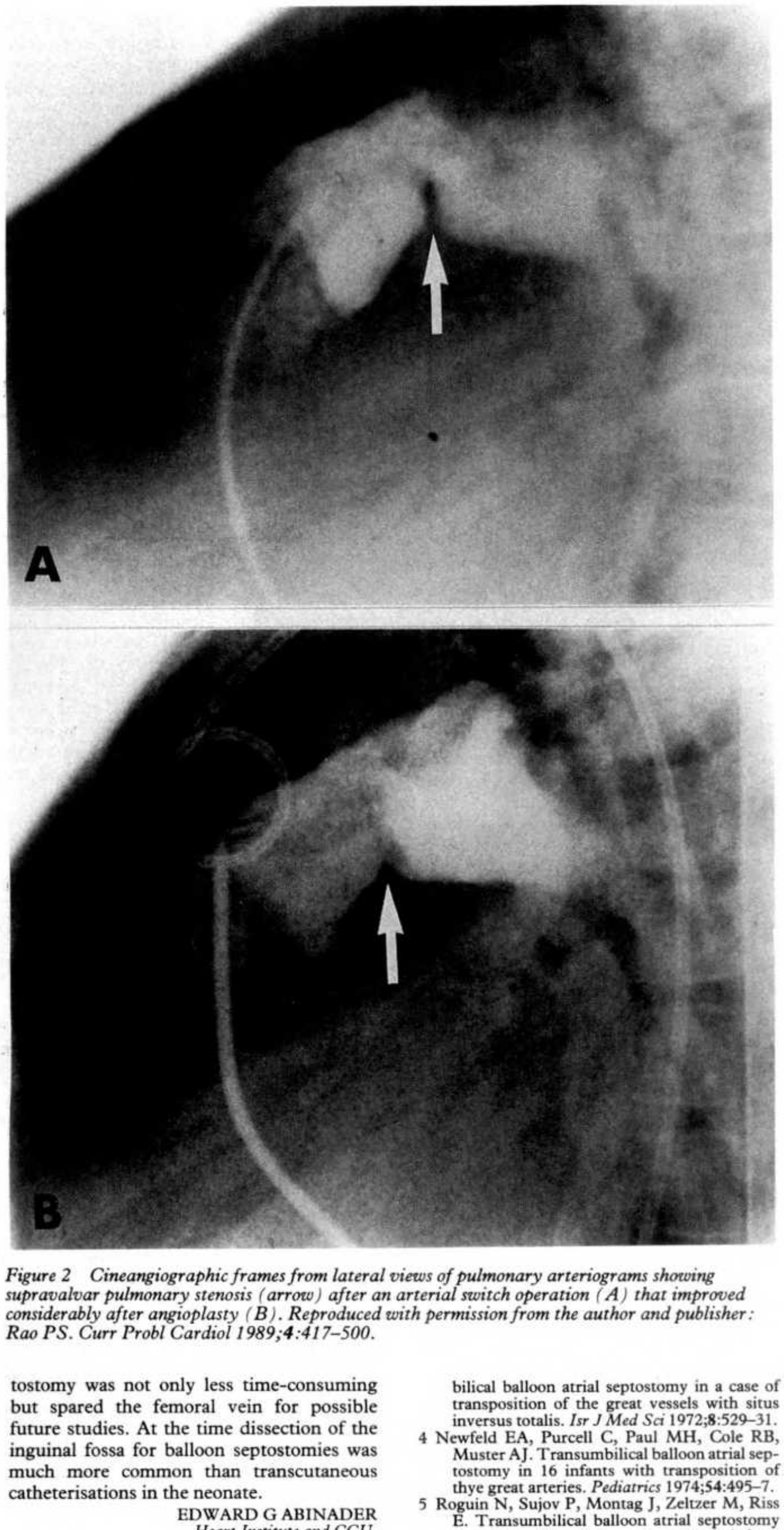

*Figure 2 Cineangiographic frames from lateral views of pulmonary arteriograms showing supravalvar pulmonary stenosis (arrow) after an arterial switch operation (A) that improved considerably after angioplasty (B). Reproduced with permission from the author and publisher: Rao PS. Curr Probl Cardiol 1989;**4**:417–500.*

tostomy was not only less time-consuming but spared the femoral vein for possible future studies. At the time dissection of the inguinal fossa for balloon septostomies was much more common than transcutaneous catheterisations in the neonate.

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1 Ashfaq M, Houston AB, Gnanapragasam JP, Lilley S, Murtagh EP. Balloon atrial septostomy under echocardiographic control: six years' experience and evaluation of the practicability of cannulation via the umbilical vein. *Br Heart J* 1991;**65**:148–51.
2 Abinader E, Zeltzer M, Riss E. Transumbilical atrial septostomy in the newborn. *Am J Dis Child* 1970;**119**:354–6.
3 Romney D, Katzuni E, Aygen MM. Transumbilical balloon atrial septostomy in a case of transposition of the great vessels with situs inversus totalis. *Isr J Med Sci* 1972;**8**:529–31.
4 Newfeld EA, Purcell C, Paul MH, Cole RB, Muster AJ. Transumbilical balloon atrial septostomy in 16 infants with transposition of thye great arteries. *Pediatrics* 1974;**54**:495–7.
5 Roguin N, Sujov P, Montag J, Zeltzer M, Riss E. Transumbilical balloon atrial septostomy for transposition of the great arteries in infants under the age of 60 hours. *Am Heart J* 1984; **107**:174–6.
6 Kaye HH, Tynan M. Balloon atrial septostomy via the umbilical vein. *Br Heart J* 1974; **36**:1040–2.

SIR,—The report of balloon atrial septostomy under echocardiographic control by Ashfaq *et al* makes interesting reading but certain points need to be clarified before recommending it as a procedure of choice.

On the basis of the size of the atrial septal defect they created (as seen on echocardiographic image or by colour flow mapping) Ashfaq *et al* claim that the procedure was successful. However, though they believe that such a defect can be "accurately measured" on echocardiography, they do not give the values (mean (SD)) of the defect size or flow jet width. In another study adequately palliated neonates had a post-septostomy interatrial defect of at least 12 mm in diameter as measured angiographically[1] or later at surgery or necropsy.[2] In most of the previous series, satisfactory early improvement after atrial septostomy has been defined as either an increase in oxygen saturation of greater than 10% with reduction in interatrial mean pressure gradient to less than 2 mm or arterial saturations of greater than 50–75%.[3] Satisfactory late improvement has been defined as survival to six months with oxygen saturation at 60% or higher.[3] It is surprising that none of these indices are mentioned in the results though Ashfaq *et al* call their procedure "100 per cent successful". It is possible that these indices were not measured when the procedure was performed as an emergency measure. But Ashfaq *et al* do not give a break down of the number of procedures performed in an equipped catheterisation laboratory compared with those performed elsewhere or in the ward side room. The size of the post-septostomy inter-atrial defect can be measured only approximately by echocardiography.[4] We were able to image a flapping torn septum primum as an indication of an adequate septostomy. Because there are so few data on the features and limitations of echocardiography and colour flow mapping in evaluating the adequacy of post-septostomy interatrial defects, we expected that Ashfaq *et al* would have clarified these before drawing conclusions and inferences. At least the echocardiographic size of the defect could have been compared with the actual measurement at necropsy in the two patients who died.

Ashfaq *et al* seem to exaggerate the complications related to fluoroscopically guided septostomy by quoting a single reference dating back to 1970 that describes 26 cases.[5] In a more recent series of 43 infants with *d*-transposition of the great arteries studied over five years, fluoroscopy guided balloon atrial septostomy was not associated with any deaths or mechanical complications.[3] Moreover, though they do not state the average procedure time, Ashfaq *et al* presume that the echoguided procedure is less time-consuming.

Thus balloon atrial septostomy under echocardiographic guidance could be recommended during emergencies or in the catheterisation laboratory for facilitating the balloon positioning, especially in cases with cardiac malposition, but until our questions are answered it should not be advocated as a better alternative to fluoroscopy.

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1 Baker F, Baker L, Zoltun R, Zuberbuhler JR. Effectiveness of the Rashkind procedure in transposition of the great arteries in infants. *Circulation* 1971;**43–44** (suppl I):1–6.
2 Powell TG, Dewey M, West CR, Arnold R. Fate of infants with transposition of the great arteries in relation to balloon atrial septostomy. *Br Heart J* 1984;**51**:371–6.
3 Henry CG, Goldring D, Hartman AF, Weldon CS, Strauss AW. Treatment of d-transposi-

tion of the great arteries: management of hypoxemia after balloon atrial septostomy. *Am J Cardiol* 1981;47:299–306.
4 Allan LD, Leanage R, Wainwright R, Joseph MC, Tynan M. Balloon atrial septostomy under two dimensional echocardiographic control. *Br Heart J* 1982;47:41–3.
5 Venables AW. Balloon atrial septostomy in complete transposition of great arteries in infancy. *Br Heart J* 1970;32:61–5.

These letters were shown to the authors, who reply as follows:

SIR,—We agree entirely with Dr Abinader's comments. Neither the use of ultrasound imaging nor the umbilical vein route are new techniques for the performance of an atrial septostomy and in our paper we did not intend to suggest that this was the case. The initial intention was to review our experience with the efficacy of ultrasound imaging. In most centres the umbilical route has not been used routinely in the past because of difficulty in catheter manipulation where a full catheterisation is necessary to establish the diagnosis. Catheterisation is now necessary only for the performance of a septostomy and the umbilical route is ideal for this. We thought it appropriate to add our experience of the use of the umbilical route pioneered by Abinader *et al* because we were aware that many centres still did not use it.

We referred in some detail to the different workers who have commented on the ultrasound technique, which has become popular only in recent years. The use of the umbilical vein technique has been known for over 20 years and indeed it was described in 1985 in a major textbook on paediatric cardiology to which we referred.[1] We thus considered it was not necessary to refer in detail to the initial reports on this, and we agree it would have been appropriate to quote the early paper on the subject.

We would like to take the opportunity of stating that we are no longer sure of the accuracy of the comment that the ultrasound image is of little value in the manipulation of the catheter. In a newborn the heart was only entered after the image had been used to ensure that the catheter was inserted with the bend aligned in a posterior and inferior direction and then, at the appropriate point as determined from the image, it was turned through a 180° angle to pass through the ductus venosus and into the inferior vena cava and thence the heart.

Drs Kerkar and Dalvi question the validity of our supposition that a septostomy performed under ultrasound is as effective as one performed under fluoroscopy. Ours was a retrospective study and the size of the defect was not measured routinely. As their letter points out the "success" of a septostomy is difficult to define and there is more to it than simply the size of the defect. Because elective arterial switch procedures are performed within the first weeks of life data on long-term follow up can no longer be obtained. None of our patients required "emergency" surgery but in some prostaglandin therapy was continued or started after septostomy. The comment that "the size . . . showed the procedure was successful" was made on the basis of seeing a tear, a flapping septum, and an increase in the size of the defect. If the criticism is related to the use of ultrasound I cannot accept that there is any reason that the result could be different because the actual technique of pulling the catheter is no different with ultrasound or screening. We have not compared the results of using the umbilical and femoral routes but both have been accepted techniques for years. The facilities of a catheterisation laboratory are not needed for septostomy under ultrasound screening. In our paper we stated that for 10 months the ward side room was used when catheterisation facilities were unavailable; thereafter we have used the catheterisation laboratory routinely simply as a matter of convenience to the nursing staff; the *x* ray imaging facilities are not used. Where necessary septostomy is undertaken in the ward, intensive therapy unit, or maternity hospital. The location is simply a matter of personal choice and hospital routine and again I cannot suppose that there is any reason that the result would be different for ultrasound and fluoroscopy.

I accept that in experienced hands the risk of mitral damage is almost negligible—but reports attest to the fact that damage does occur with fluoroscopy. I am unaware of this happening with ultrasound screening. In addition I accept that there should be little difference in the time of the procedure whether ultrasound or fluoroscopy is used. In the past there might have been a potential delay in obtaining the services of a radiographer or access to a catheterisation laboratory in an emergency, but this is now of less concern because the infant can be maintained on prostaglandins and the septostomy performed at a convenient time.

Thus I agree with some of Drs Kerkar and Dalvi's comments but I disagree with the conclusion to their letter. In our centre the simplicity and convenience of ultrasound quickly made it the technique of choice. A preference for ultrasound or fluoroscopy may simply be a matter of personal choice, experience with ultrasound, and the hospital facilities available. However, my colleagues and I firmly believe that it is correct to advocate ultrasound as a more convenient and better imaging technique than fluoroscopy.

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1 Cardiac catheterisation and angiocardiography. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, *Paediatric cardiology*. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1987:372.

Cardiac catheterisation with 5 French catheters

SIR,—In his letter commenting on the use of 5F catheters for coronary angiography, Dr Raphael calls for further randomised studies to compare the latest 5F catheters with conventional 7F catheters (*British Heart Journal* 1991;66:114). He and your readers may be interested to know that such a trial was undertaken in Bristol using the types of 5F catheter available in 1988 and 1989.[1] The full results of this trial are due to be published soon in the *International Journal of Cardiac Imaging;* however, the main message of the trial was that the 5F catheters available at that time proved extremely unsatisfactory for coronary angiography and could not be recommended for routine use. Catheter design has progressed rapidly, or at least so we are told by the catheter manufacturers. It may be that the time is now right for a further randomised study to compare the current generation of 5F catheters with conventional catheters. Such a study will need to include not only subjective assessments of catheter performance but will also need to document objective measures of catheter performance such as procedure time, injection pressures, and incidence of significant complications.

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1 Brown E, Morris K, Wild RPH, Hartnell GG. Limitations in the performance of 5-F coronary catheters in routine angiography [abstract]. *Clin Radiol* 1989;40:648.

Genesis of Still's innocent systolic murmur

SIR,—The recent publication of the paper on Still's innocent systolic murmur[1] prompted queries about who Still was and whether Still's disease commemorates the same individual.

George Frederic Still was indeed the author of early descriptions of both conditions. His personal history has been elegantly described by Hamilton.[2] Still was educated at Caius College, Cambridge, qualified in medicine at Guy's Hospital in 1893 and, after posts at the Hospital for Sick Children, Great Ormond Street, was appointed to the first chair of paediatrics in London, at King's College Hospital, in 1906. His publications included five books and 108 papers,[3] among the earliest being his classic description of the form of chronic arthritis in childhood that bears his name.[4]

In his book *Common Disorders and Diseases of Childhood*[5] the innocent systolic murmur is referred to as a "physiological bruit" which must be differentiated from the "sometimes musical character of murmurs occurring in bacterial endocarditis". He describes the innocent murmur in these terms: "It is heard usually just below the level of the nipple, and about half way between the left margin of the sternum and the vertical nipple line; it is not heard in the axilla nor behind; it is systolic and is often so small that only a careful observer would detect it; moreover, it is very variable in audibility...; its characteristic feature is a twanging sound, very like that made by twanging a piece of tense string". This description remains accurate and authoritative to this day.

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1 Gardiner HM, Joffe HS. Genesis of Still's murmurs: a controlled Doppler echocardiographic study. *Br Heart J* 1991;66:217–20.
2 Hamilton EBD. George Frederic Still. *Ann Rheum Dis* 1986;45:1–5.
3 Franklin AW. A handlist of the writings of George Frederic Still. *Arch Dis Child* 1941; 16:154–5.
4 Still GF. On a form of chronic joint disease in children. *Med-Chir Trans* 1897;80:47–59.
5 Still GF. Common disorders and diseases of childhood. 3rd ed. London: Oxford University Press, 1920:495.

Is cardiac rehabilitation necessary?

SIR,—Precise identification of the specific needs of individual coronary patients for rehabilitative care and precise recommendations regarding the components of this care will enable precise assessment of the outcomes of these interventions.

The occurrence of a coronary event and/or the performance of a myocardial revascularisation procedure (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) indicates that advanced coronary atherosclerosis is present. Provision of optimal care for these coronary patients in the 1990s includes identification of the specific needs of that individual patient for the prescriptive exercise training and education and counselling to help to remedy the disease. Recommendations for rehabilitative care may include a structured supervised program, exercise at home or unsupervised exercise, counselling by physicians and/or other health professionals, or the use of contemporary technological aids such as videotapes to guide home exercise or computer-interactive educational programs to provide information and counselling.[1] Exercise training as prescription rather than proscription is often the point of entry to rehabilitative care that facilitates adoption of health-related behaviours.

Education and counselling involve not only the provision of information but also training in the skills needed to improve health-related behaviours, practising these skills, and reinforcement of successful changes in coronary risk status. Appropriate provision of cardiac (coronary) rehabilitation includes selection of the relevant components and the method of delivery for an individual patient, definition of the desired outcome, and delineation of the time frame in which this outcome is expected to occur.

Exercise training, designed to decrease activity-induced symptoms and improve functional capacity, should be evaluated by this outcome measure, rather than by any effect of exercise on coronary risk reduction, psychosocial status, return to work etc. Although improved survival was a goal of exercise rehabilitation in the early 1970s, contemporary medical and surgical treatments have improved outcome so much that any added intervention is unlikely to improve survival further. The benefits of supervised and unsupervised exercise have not been compared in a randomised fashion, but for low risk patients unsupervised modest intensity exercise training may be more easily adhered to than the higher intensity supervised exercise regimens, which produce more musculoskeletal discomfort and are less convenient; this requires evaluation. As noted by Dr Lipkin (*British Heart Journal* 1991;65:237–8) the availability of risk stratification procedures and the documented efficacy of low intensity exercise permits this physician-directed exercise rehabilitation outside a structured supervised program. "Formal" exercise programmes (that is, individually prescribed exercise with instructions for implementation) are appropriate for most coronary patients. However, supervised and particularly electrocardiographically monitored exercise rehabilitation should be limited to selected patients.

Improved psychological function as an outcome of rehabilitative care should be assessed only among coronary patients who have identified psychosocial problems and for whom specific interventions are recommended. It should not be expected to come simply from participation in an exercise regimen.

Unfortunately, the "usual" supportive care may not include adequate multifaceted education and counselling, which often require considerable time and specialised knowledge—teaching dietary modification is a good example of this. However, the specific goals set for each educational component can provide a standard against which to evaluate outcome.

Perhaps analysis of the benefits of cardiac (coronary) rehabilitation are hampered less by the heterogeneity of the patients than by the heterogeneity of the questions asked.[2] An optimal regimen (rather than an inflexible programme) of rehabilitative care should be defined by the patient's physician, in consultation with the patient (and programme staff if a structured supervised programme is chosen). If suitable rehabilitative services are selected and the desired mode of implementation and expected outcome are defined for each component, the validity and efficacy of rehabilitative interventions can be assessed.

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[1] Wenger NK. Rehabilitation of the coronary patient: A preview of tomorrow. *J Cardiopulmonary Rehabil* 1991; 11:93.

[2] Wenger NK, Alpert JS. Rehabilitation of the coronary patient in 1989. *Arch Intern Med* 1989;149:1504.

Sir,—Dr Lipkin quite rightly defines cardiac rehabilitation "as a process by which patients with cardiac disease are restored to their optimal physical, medical, psychological, social, emotional, vocational and economical status" but in later remarks he seems to equate this process to one of physical training. Is it realistic to think that physical training alone can bring it about? Obviously it is not. Organised motor activity it is quite properly called "physical exercise" or, when it is designed to induce specific biological changes, "physical training". But this is a far cry from rehabilitation, which, as Lipkin himself reminds us, is a complex combination of medical and non-medical measures rendered much better by a term such as: "prognostic evaluation and long-term care". In other words the focus of rehabilitation is the chronically ill patient.

Chronic heart failure is a case in point. At a few cardiac rehabilitation units much of the cardiologists' time is taken up with the care of patients awaiting transplantation—care that encompasses pharmacotherapy, detection and treatment of metabolic abnormalities, nutritional support, regimens to prevent physical deconditioning, prophylaxis against infections, support replacing temporary loss of physiological functions (ultrafiltration, mechanical ventilation) attention to the sleep-wakefulness rhythm, detection and elimination of any possible causes of disease progression, the caring and compassionate counselling which can be of vital importance in many cases.

I do not know whether "rehabilitation" is a fitting term to cover the range of care from the soft follow up of uncomplicated post-infarct patient on a secondary prevention programme and the semi-intensive care of chronically, critically ill patients and I am certainly not claiming that such wide-ranging, complex undertakings should be simply assigned to the present rehabilitative facilities.

However, we have to recognise that new realities, such as longer life expectancy and effective treatment, together with the chronic nature and long duration of most cardiac diseases (ischaemic heart disease, myocardiopathies, "essential" hypertension and so forth), tend to increase their prevalence. The course of these diseases, mostly silent until an explosion of symptoms with often irremediable damage suggests that the logical approach is to make every effort to prevent acute episodes—that is, by controlling disease progression by careful chronic care and by managing recovery after unprevented episodes in order to preserve the patient's autonomy and quality of life. The health service as at present structured, focused on hospitals, is concerned primarily with resolving diagnostic problems and coping with emergencies rather than with the systematic follow up of the chronic patient. In most countries rehabilitation is in embryo and still lacks a coordinated professional approach to the chronic cardiac patient's problems, but it is the first serious attempt at a comprehensive and permanent approach to these patients.

Several current papers refer to rehabilitation as "physical training", I believe this to be an oversimplified and rather confusing view that should not be reinforced in editorials written by authoritative persons for authoritative journals.

LUIGI TAVAZZI
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These letters were shown to the authors, who reply as follow:

Sir,—I agree with Professor Tavazzi's comments. We do tend to concentrate on physical rehabilitation because changes in effort tolerance are more easy to measure than the psychological and emotional responses to the treatment, which often improve with improvement in physical exercise capacity. Whether one wishes to call the post-hospital follow up and treatment of patients "rehabilitation or prognostic evaluation and long term care" is arguable. I agree that the supportive care many patients require includes "multi-faceted education and counselling". An optimal regimen tailored to the patient's requirements would be ideal as I mentioned in my editorial, but as Douglas Chamberlain and his colleagues recently commented it is obvious that cardiological resources in the United Kingdom are so restricted that at present this ideal might not be met.[1]

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[1] Chamberlain D, Pentecost B, Reval K, Stevens J, McC Boyle D, Cobbe S, Ballantyne D, Shaw T. Staffing in cardiology in the United Kingdom 1990: sixth biennial survey: with data on facilities in cardiology in England and Wales 1989. *Br Heart J* 1991;66:395–404.

BOOK REVIEW

Cardiomyoplasty. Eds Alain Carpentier, Juan Carlos Chachques, and Pierre Grandjean. (Pp 280; $85·00.) Mount Kisco, NY: Futura Publishing Company, 1991. ISBN 0-87993-395X.

Two of the editors of this book, Alain Carpentier and Juan-Carlos Chachques, surgeons from Hôpital Broussais in Paris reported, in 1985, the first clinical use of latissimus dorsi muscle to augment the left ventricle. The third editor, bioengineer Pierre Grandjean, has made a major contribution to the pacing systems required to train and drive the transplanted and transformed skeletal muscle. Among the 50 contributors are the best known names in the field—such as the anatomist, Salmons; his surgical collaborator for many years, Larry Stephenson; and Pette who described changes in phenotype expression of muscle. The major clinical contributors to cardiomyoplasty are represented and include Magovern's group from Allegheny, and Jatene and colleagues from São Paulo, Brazil who, with the Paris surgeons have provided the major part of the world's clinical use of the technique. The monograph is authoritative, comprehensive, beautifully produced, generously illustrated, and very readable. It is based on papers presented at a Paris meeting in June 1989 at which time there were about fifty patients. Papers from another international meeting in October 1990, from the same principal authors, reviewing double the number of patients, had already appeared in April 1991 in *Seminars in Thoracic and Cardiovascular Surgery,* months before this hardback volume was released. This book may be seen as a landmark but it does illustrate the difficulties, acknowledged by Alain Carpentier in his insightful foreword, of publishing in a rapidly changing field.

TOM TREASURE

The title reviewed here is available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

BRITISH CARDIAC SOCIETY NEWSLETTER

The last newsletter gave the up to the minute news of completion of our purchase of our own property at 9 Fitzroy Square. By the time this appears we should be well settled in the new house. It is a fine Georgian building ideally suited to the new and expanding activities of the society. The offices of the *British Heart Journal* will share the premises—an ideal arrangement given our close working relationship. Our affiliated groups and societies have all expressed an interest in making use of the new facilities. We have rooms large enough not only for all the committees, but also for our planned teach-ins, and for workshops if plans for these are approved. Kitchen facilities are available, so that catering on the premises becomes a possibility. We hope that the house will become a well integrated headquarters for all major activities relating to the British Cardiac Society. To achieve this we will, of course, require additional staff. Mrs Elaine Brown (our administrator), and Mrs Jenny Lodge (our assistant administrator and bookkeeper) have coped so far with all the affairs of the society—with assistance from Sussex for secretarial work and surveys. We have enrolled a new part-time secretary in London, and further changes may follow if the workload grows. If any members of the society find themselves near Fitzroy Square, we hope they will call in: it is only minutes from the Royal College of Physicians, and from Regents Park, Great Portland Street, Euston Square, and Warren Street Underground Stations.

The meeting organised by the society on the developing internal market in cardiology and cardiac surgery was held at the Royal College of Physicians on 4 December. It was well attended with over 200 delegates; 40% were cardiologists or cardiac surgeons, 30% were managers from provider units, and 30% came from purchaser health authorities. The speakers included a regional director of public health, a health economist, five clinicians (of whom one was American), and representatives of the NHS Management Executive and the Department of Health. The initial presentations dealt with the future management of regional specialties and with modelling of treatment patterns of coronary artery disease—with economic evaluation of outcomes. The experience of three clinicians was reported, and the requirements were discussed for refining case mix and coding for effective setting of contracts. The difficulties ahead seem formidable, and the market seems likely to be managed centrally for some time to come. The meeting finished with a session looking at supraregional specialties and clinical research. Their future was linked to the research and development initiatives that are being developed by the NHS Management Executive. A full report is being prepared—and should be a valuable source of information in a difficult and new area. We will let you know later how this can be obtained.

A meeting of representatives of the affiliated groups was held at the British Cardiac Society on 29 November. Representatives from the British Cardiovascular Intervention Society (BCIS), the British Paediatric Cardiac Association (BPCA), the British Society of Echocardiography (BSE), the British Nuclear Cardiology Group (BNCG), and the British Pacing and Electrophysiology Group (BPEG) all expressed an intention for the groups to be recognised as part of the British Cardiac Society, while retaining their autonomy within the individual organisations. This position has not previously been defined in any formal way, and the word "affiliated" had been open to varying shades of interpretation. The groups will want to confirm their positions after appropriate discussions, but in the meantime they were invited to submit a statement of the support they may wish to receive from the British Cardiac Society. This task has to be undertaken with some urgency, so that we can make the best use of 9 Fitzroy Square. Possible financial support, record keeping, secretarial assistance, data collection, audit, relations with European societies, management of any subscriptions, space for small meetings and arrangements for large ones, printing, and publications—these should all be considered. The special position of the British Nuclear Cardiology Group was recognised; most of its members are not cardiologists. This was not seen as an overriding difficulty: this group can be affiliated under the same arrangements as the other groups.

Arrangements for the Harrogate meeting are almost complete. Dr Eugene Braunwald has agreed to give the Sir Thomas Lewis lecture; Dr Lars Ryden will be the non-United Kingdom (how else these days do we say "European"?) judge for the Young Research Workers Prize; and we are planning a partners programme. Simultaneously with the young research workers presentations we will have—as an experiment—a session designed for state-of-the-art presentations designed to suit the needs of district hospital cardiologists.

We hear that some district hospital cardiologists have felt that the society does not cater adequately for their needs. If the society has shown a bias towards matters of concern to cardiologists in the major centres, this is not intentional. We believe that the impression reflects an earlier pattern of activities that were entirely appropriate when district hospitals had few specialist physicians, and that this view is increasingly outmoded. If we can do more for district cardiologists—who face so much of the burden of heart disease—then please make suggestions; they will be welcome. We do wish to see more colleagues from outside the major centres proposed for and elected to council.

New proposals for the constitution will come before the Annual General Meeting in Harrogate. Some have already been widely discussed: that council should include a representative from paediatric cardiology and that the chairman of the cardiology committee of the Royal College of Physicians and the society's own Postgraduate Cardiology Advisor should also be on council. A more recent suggestion that also seems to have much merit relates to the officers: that in future the president should serve for two years rather than three, and that the president-elect is also in post for two years. Thus there will always be five officers. While future presidents will still have a total of four years in office, the load will be more evenly spread.

The December newsletter referred to the possibility of a meeting to discuss the future of arrhythmology units, with special reference to the funding of an important growing point of cardiology. Proposals put to the cardiology committee earlier in 1991 were not adopted, pending further discussions among interested parties: the society in cooperation with BPEG is clearly an approprate forum for these. A provisional date of 10 March has now been agreed. We believe that representatives from the Department of Health may be willing to join us.

The British Cardiac Society and the Society of Cardiothoracic Surgeons wish to implement a new scheme to make information cards available to all patients with replacement heart valves (newsletter, September 1991). This would be based on the United Kingdom valve registry organised by Ken Taylor at Hammersmith Hospital. We are hopeful that the valve manufacturers will be willing to provide the modest support needed for this project, though negotiations have taken longer than we expected. In the meantime, Shiley have arranged that the Medic Alert Foundation should cooperate with our societies to make bracelets available to any patients with the Björk-Shiley convexo-concave valves that may be at risk of strut fracture. A letter about free registration with Medic Alert has been sent to at least one cardiologist (or physician with an interest in the specialty) in every hospital that may treat such patients. To retain the confidentiality of our database we undertook the mailing ourselves.

Do not forget the date for our first teach-in, announced in the December newsletter. This new programme is intended to update members of the society in growing points of modern medicine that are intimately related to our specialty. Sir David Weatherall will be arranging the first meeting (on molecular biology) on Tuesday 31 March from 10 am to 4 pm. A subsidy will be available for long-distance travel within the United Kingdom. We intend that these meetings should be small to encourage interaction with the speakers. There will not be another similar opportunity for a very long time. Contact the society at once if you wish to reserve a place—but you may already be able to secure a place on the reserve list only . . . Please note that the meetings are exclusively for members.

Copies are now available from the society offices of the Fourth Report of a Joint Cardiology Committee of the Royal Colleges of Physicians of London and the Royal College of Surgeons of England on the provision of services for the diagnosis and treatment of heart disease. The college reports are authoritative documents that can be of great value to those who have to persuade managers of the basic requirements of a cardiology service.

Another date for many diaries, and again we expect demand to exceed supply: Resuscitation '92 will be the first CPR congress of the European Resuscitation Council (the British Cardiac Society was prominent in the formation of the European Resuscitation Council which is now gaining wide acceptance in Europe). An excellent international programme has been arranged in cooperation with the Resuscitation Council of the United Kingdom. The meeting will take place in the Brighton Centre. All the indications show this will be a popular meeting and many delegates are expected from mainland Europe. Application forms can be obtained from the society office.

Remember to note our new address given below. And again for reference our new telephone number is: 071 383 3887. Note that our fax number has a slightly different exchange code: 071 388 0903.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
9 Fitzroy Square,
London W1P 5AH

NOTICE

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts was 3 January.

CORRECTIONS

Staffing in cardiology in the United Kingdom. Sixth biennial survey: with data on facilities in cardiology in England and Wales 1989 (November issue, volume 66: pages 395–404). The President of the British Cardiac Society has asked us to point out that table 13 showed an incorrect total under the number of consultants retiring from 1991 to 1995, though the data for individual years were correct. This total was inadvertently left unchanged when one year was removed from the table shortly before the paper was submitted.

Table 16 showed the number of technicians in the Regions of England and Wales, and these figures were correct according to the returns received. But the calculations for numbers per 250 000 were incorrect—the true totals were slightly higher. This error represents a complex calculation based on the premise that the need for technician time is not related in a linear fashion to population. These figures were derived for another purpose but were inadvertently substituted for the original calculations that had been correctly made.

* * *

Physical activity in ischaemic heart disease in middle-aged British men. *AG Shaper, G Wannamethee* (November issue, volume 66: pages 384–94). The authors have asked us to point out that R Weatherall was inadvertently omitted from the authorship of this paper, which is *AG Shaper, G Wannamethee, R Weatherall.*

As a service to readers each month the *British Heart Journal* publishes a list of the current contents of *Cardiovascular Research*, a sister journal published by the BMJ Publishing Group in association with the British Cardiac Society.

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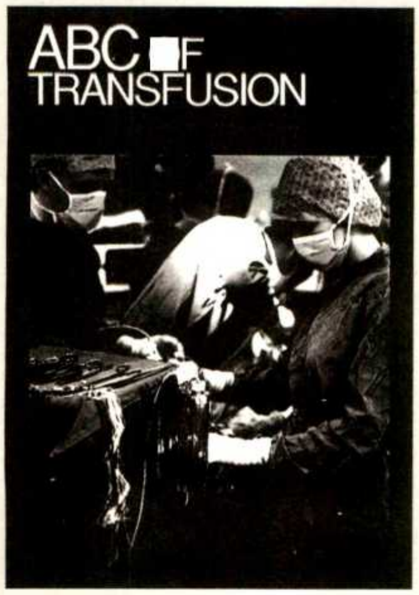

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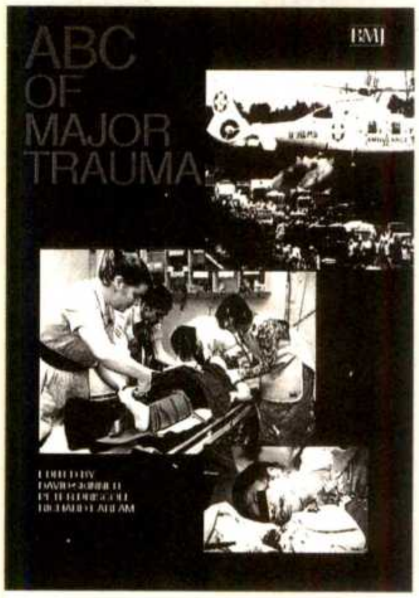

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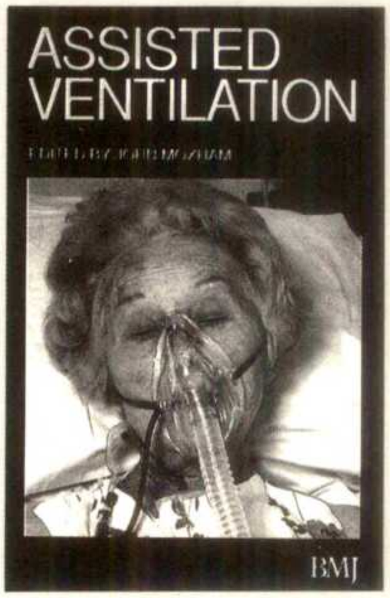

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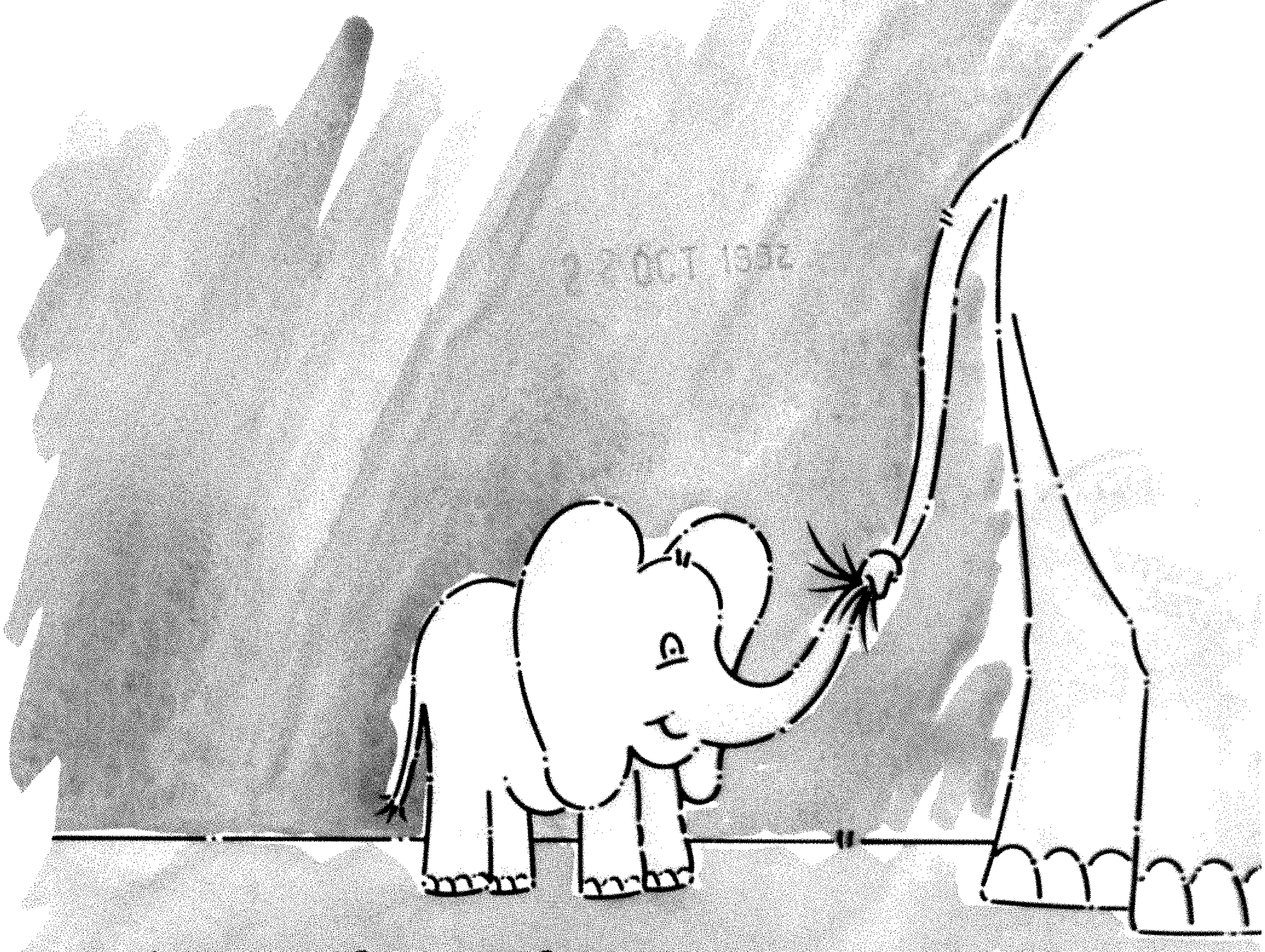

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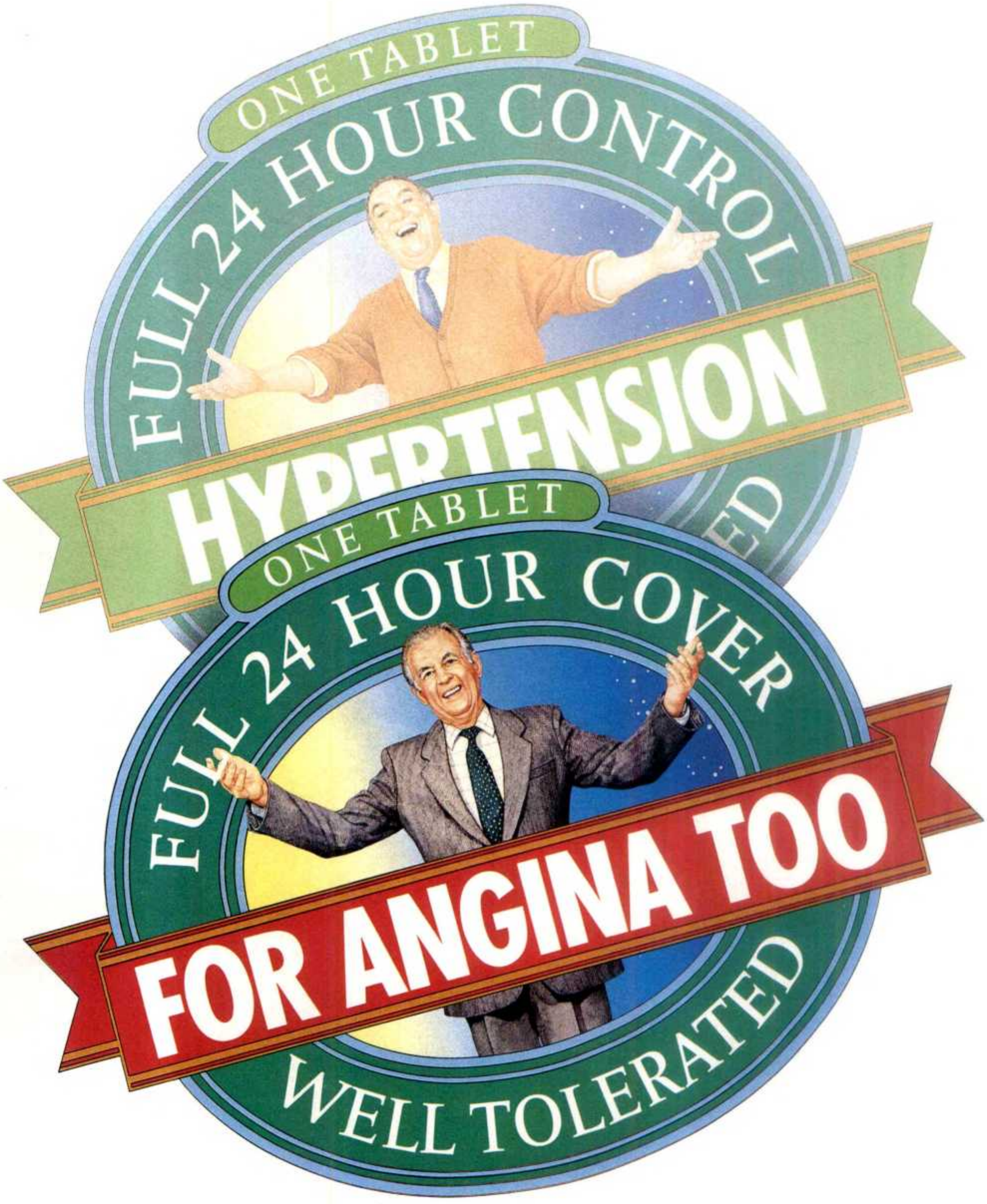

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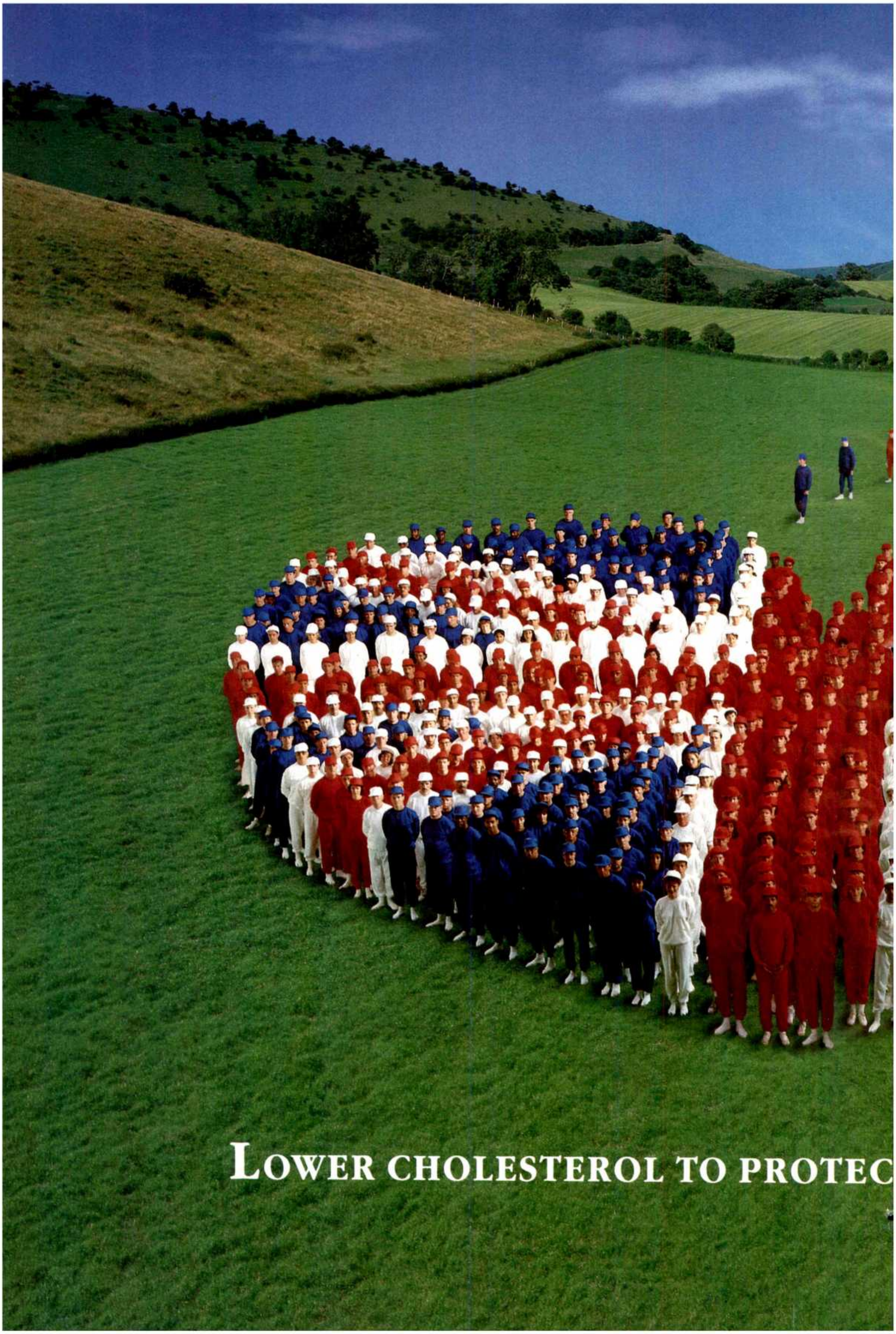
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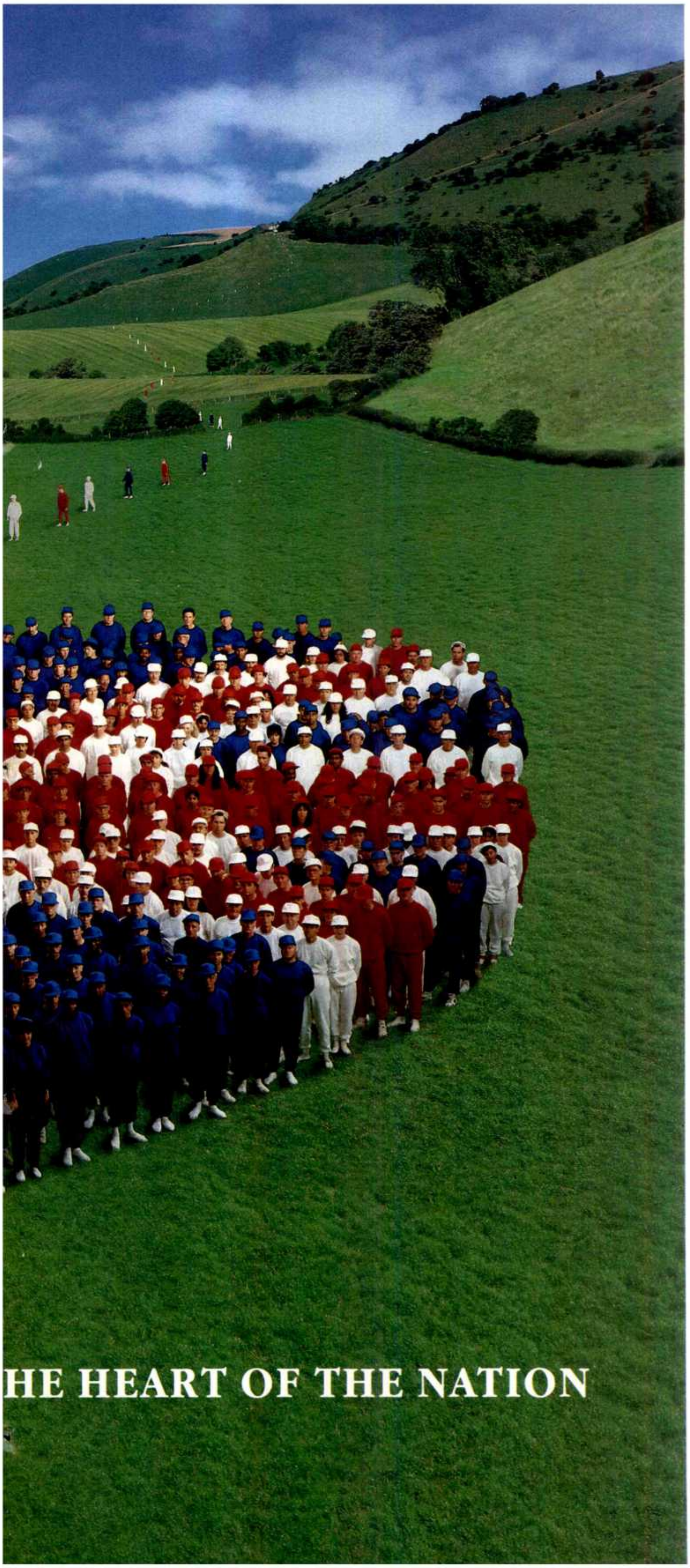
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1. OPCS Monitor DH2, June 1990.
2. Lipid Research Clinics Program, *J. Amer. med. Ass.*, 1984, **251**, 351.

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Editorial

Stent implantation in congenital heart disease

Intravascular stents are increasingly being used to maintain vessel patency in peripheral and coronary arteries.[1,2] Lately their use has been extended to treat patients with congenital heart disease. O'Laughlin and colleagues reported on 30 patients in whom 45 stents were implanted with encouraging short-term results.[3] A paper on page 240 of this issue and two earlier case reports extend the range of congenital heart defects for which stents will be useful.[4-6]

Mulcahy *et al* reported clinical improvement after implantation of a self expanding stent in a patient with stenosis of a pulmonary artery branch that was resistant to balloon dilatation.[4] O'Laughlin implanted 36 balloon expandable stents in 23 patients with pulmonary artery stenoses: 22 of them had had operations for other lesions.[3] The mean systolic gradient fell from an average of 51 mm Hg to 16 mm Hg and the vessel diameter of the stenosis doubled. More importantly, O'Laughlin *et al* showed redistribution of blood flow to the previously hypoperfused lung in those patients in whom perfusion was measured. One patient died after the procedure when a right atrial thrombus occluded his Fontan circulation. In two patients the stents were misplaced—in one the stent passed too far distally down the pulmonary artery and could not be retrieved. It was expanded there and when a second stent was placed more proximally at the lesion site the clinical result was good. In the second patient the stent could not be placed correctly in the distal right ventricular outflow tract and had to be removed surgically from the right ventricle. A branch of the pulmonary artery was ruptured after balloon dilatation but this did not preclude subsequent stent implantation. While in most patients flow into side branches covered by the stent was not impaired, in two patients the right upper lobe branch was partially obstructed, possibly by compression of the ostium. Mulcahy *et al* described a further complication, that of transient pulmonary oedema secondary to high flow into the lung segment perfused through the stent; but this has also been seen after balloon dilatation alone.[4]

The Senning and Mustard operations for complete transposition may be associated with obstruction to the systemic venous pathways. Though the superior caval pathway is more commonly the obstructed pathway, occasionally both the systemic pathways can become obstructed and in an extreme form this can cause a debilitating protein-losing enteropathy. Balloon dilatation of the narrowed pathways can be effective but in these large calibre, low pressure vessels, large balloons are required to achieve a satisfactory result.[7] Recoil of the stenosis is not uncommon and balloon dilatation is ineffective if the pathway is kinked. Chatelain *et al* have highlighted the important benefit that stents can produce in this situation.[5] It is encouraging to note that patency of the pathways was well maintained 11 months after the procedure and after anticoagulation for the initial three months. O'Laughlin *et al* also used stents in the large venous pathways that form part of the Fontan circulation. Good results were achieved in five patients but follow up was much shorter.

Implantation of stents into the arterial ducts of sick neonates is likely to be technically more demanding than implantation in larger patients. These difficulties are highlighted by Gibbs *et al* in this issue.[6] They used this procedure as a palliative treatment in two patients with duct dependent cyanotic heart disease.[6] It is vital to implant the stent or stents to cover the whole length of the duct without protruding into either the pulmonary artery or aorta. The variable tortuosity and length of the arterial duct can hamper accurate identification of its exact limits. This difficulty is increased by the distortion and displacement caused when rigid catheters are placed across the duct. Optimal screening is essential and good radio-opacity of the stent is mandatory if the difficulties reported by Gibbs *et al* are to be avoided. In newborn lambs we found it difficult to implant poorly radio-opaque stents of the type used by Gibbs *et al* but radio-opaque stents (both balloon expandable and self expanding types) remained patent for at least nine months. We found that stent implantation was much better than balloon dilatation alone and, like Gibbs *et al*, we believe that it may avoid the need for neonatal systemic to pulmonary artery shunt operations in patients with duct dependent cyanotic heart disease. However, we witnessed the sudden death of a lamb in which the duct and stent were patent at postmortem examination. This incident and the sudden deaths in the two patients reported by Gibbs *et al* are disquieting and further evaluation is required.

Stents have also been used for palliation in patients with the hypoplastic left heart syndrome. Ruiz implanted stents in six patients in the hope of palliation until a heart transplant could be performed (personal communication). Three patients have undergone heart transplantation but the other three died. If a suitable donor heart distal does not become available those patients will need distal pulmonary artery banding or a Norwood procedure.

There has been much greater experience of stent implantation in coronary artery disease. In these patients primary stent implantation is used for lesions at high risk of restenosis or where an occlusive dissection might have catastrophic results. The duration of ischaemia produced by shorter inflation times and the immediate tacking of the dissection against the vessel wall are seen as major advantages of stents. O'Laughlin *et al*[3] used stents to tack acute balloon induced dissections in two patients in whom they had already elected to implant a stent (in a pulmonary artery branch in one, and a pulmonary artery conduit in another). In addition they also used a stent for this purpose in a patient with unexpected aortic dissection after balloon dilatation of aortic coarctation. Could primary stent implantation for aortic coarctation have advantages over balloon dilatation alone? The stents might prevent acute dissections, serve as a barrier to aneurysm formation, and reduce the recurrence rate.

To date stents have been implanted predominantly in older children and young adults in whom little or no further growth of the relevant vessels is expected. Their use in the arterial duct is a notable exception. Intravascular stents of a fixed diameter implanted into vessels that are expected to grow will eventually become rigid "stenoses" and will significantly reduce flow. Balloon dilatation might then not be effective and the only option would be surgical excision of the stent with conduit interposition. An option that must be examined is the implantation of stents with potential final diameters that are considerably larger than their diameter at implantation. Such stents could be balloon expandable or self expanding. Balloon expandable stents could then be redilated after the vessel has grown, possibly many years later. Indeed O'Laughlin *et al* were able to redilate stents after a few months but it is unlikely that the vessels had grown appreciably. They were probably simply improving an initially suboptimal result. If a self-expanding stent with a considerably greater potential diameter than the vessel itself were implanted, continued expansion of the stent could keep pace with growth of the patient and avoid obstruction. However, it is possible that in thin-walled structures, acute expansion of such an oversized stent could erode the vessel or produce an aneurysm. Furthermore, though expansion might proceed at a rate similar to the growth of the underlying vessel for a time, the stent could eventually become constrained by peri-intimal scarring. Subsequent balloon dilatation would still be needed but perhaps later than after implantation of a balloon expandable stent. We are currently investigating these issues in a growing animal model (lambs).

At present it seems sensible to restrict stent implantation to vessels that have attained their final size or have nearly done so. That stent implantation will have an increasingly useful role in congenital disease is surely not in doubt.

ERIC ROSENTHAL
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1 Palmaz JC, Richter G, Noeldge G, Schatz RA, *et al*. Intraluminal stents in atherosclerotic iliac artery stenosis: Preliminary report of a multicentre study. *Radiology* 1988;**168**:727–31.
2 Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;**316**:701–6.
3 O'Laughlin MP, Perry SB, Lock JE, Mullins CE. Use of endovascular stents in congenital heart disease. *Circulation* 1991;**83**:1923–39.
4 Mulcahey D, Sigwart U, Somerville J. Successful stenting of a life threatening pulmonary arterial stenosis. *Br Heart J* 1991;**66**:463–5.
5 Chatelain P, Meier B, Friedli B. Stenting of superior vena cava and inferior vena cava for symptomatic narrowing after repeated atrial surgery for D-transposition of the great vein. *Br Heart J* 1991;**66**:466–8.
6 Gibbs JL, Rothman MT, Rees MR, Parsons JM, Blackburn ME, Ruiz CE. Stenting the arterial duct: a new approach to palliation for pulmonary atresia. *Br Heart J* 1992;**67**:240–5.
7 Kirk CR, Gibbs JL, Wilkinson JL, Wilson N, Dickinson DF, Qureshi SA. Protein-losing enteropathy caused by baffle obstruction after Mustard's operation. *Br Heart J* 1988;**59**:69–72.

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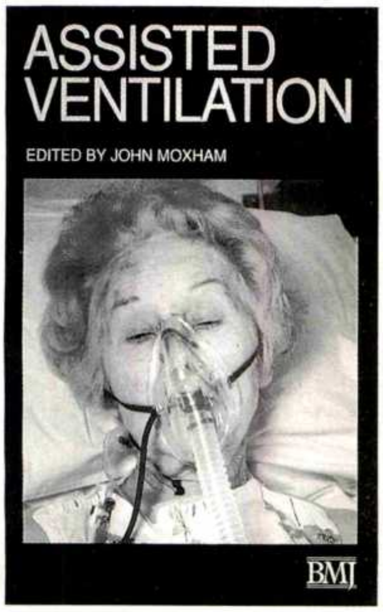

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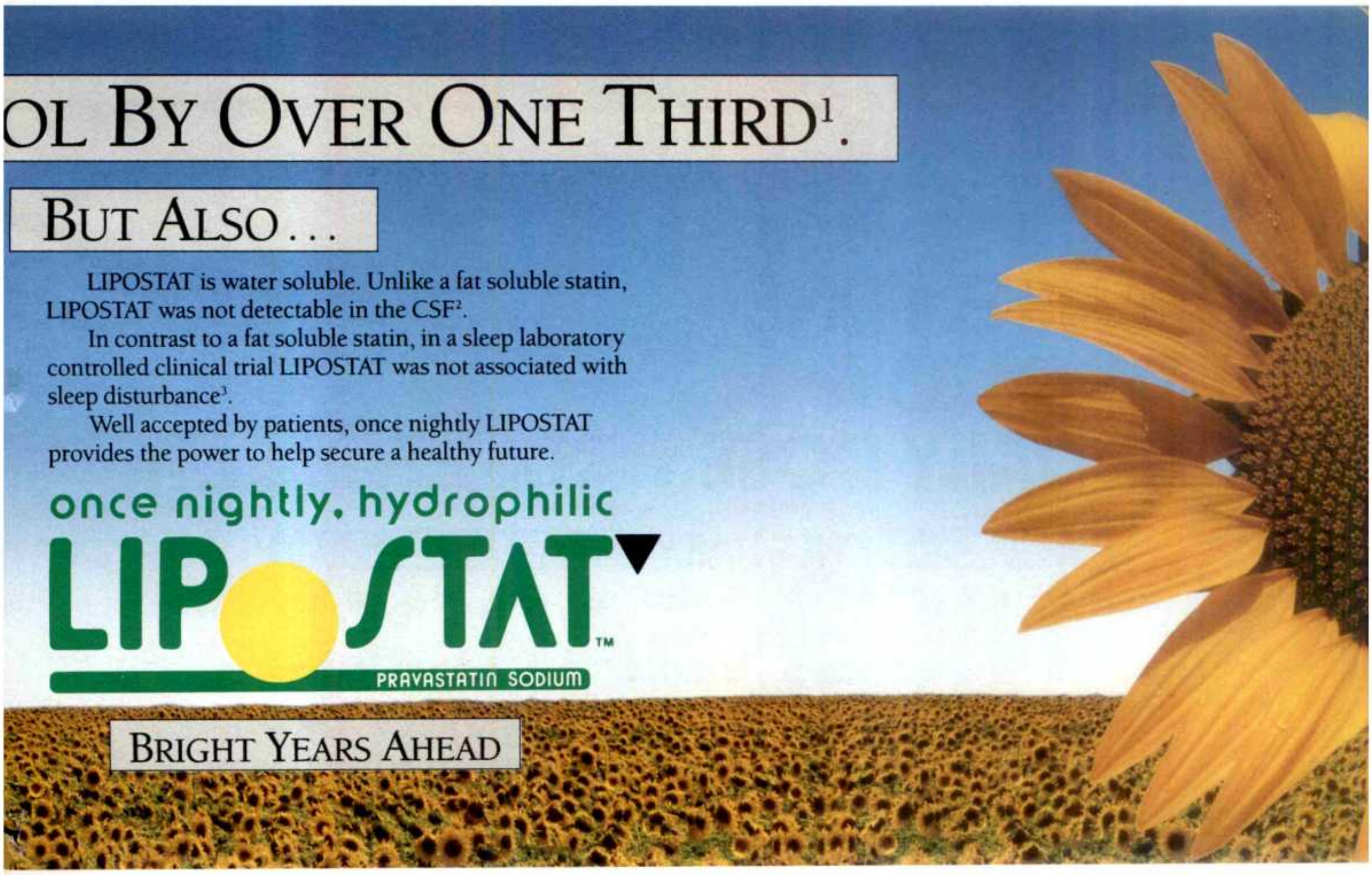

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te of Preparation September 1991

References
1. Data on file. In trials LIPOSTAT demonstrates an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).
2. Botti RE et al. Clin Neuropharm 1991, 14 (3): 256-261.
3. Bixler EO. Round Table Discussion, Lipid Management: Pravastatin and the Differential Pharmacology of HMG-CoA Reductase Inhibitors. Proceedings of a panel discussion held in London on 5th July 1989. Royal Society of Medicine Services Round Table Series 1990; 16: 32-40.

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RHÔNE-POULENC RORER

REVIEW

Interaction between ventricular loading and repolarisation: relevance to arrhythmogenesis

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Abnormality of left ventricular wall motion is a major predictor of sudden cardiac death in patients with coronary disease[1,2] or after myocardial infarction.[3,4] Death is usually caused by arrhythmia.[5] Some patients with chronic heart failure die as a result of profound bradycardia and/or asystole[6] but there is also a high incidence of lethal or potentially lethal ventricular arrhythmia.[7-10] Moreover, the incidence of ventricular arrhythmia is high in patients with hypertension,[11-13] and in patients with aortic stenosis.[14] The mechanism for the association between wall motion or mechanical load abnormality in these patients and arrhythmia is unclear. One possibility is a direct interaction between mechanical and electrical events whereby myocardial load or strain influences the electrophysiology[15]—that is, the excitability and refractoriness of the myocardial cells. Such a mechanism has been shown in isolated tissues and in animal studies[15,16] and is now receiving attention in humans.[17,18] This mechanism if present could well be implicated in the genesis of human arrhythmias[19] particularly if it could be shown that there was a differential response between areas of abnormal wall motion and normal wall motion, as has been shown in studies of dogs with chronically infarcted hearts.[20]

To date three studies in humans provide evidence for a relation between stretch or strain and the electrophysiological behaviour of myocardial cells.[17,18,21] One of these studies also shows that abnormality of wall motion can significantly modify this relation.[21]

Possible arrhythmogenic mechanisms

There are several ways by which mechanically induced electrophysiological effects may be arrhythmogenic in the clinical setting of ischaemia, acute infarction, or in hearts subject to pressure/volume overload.

MECHANICALLY INDUCED REACTIVATION

Regional asynergic or paradoxical wall motion occurs early during myocardial ischaemia.[22-24] Patients who develop an aneurysm within 48 hours—that is, an area of systolic akinesia or dyskinesia with a distinct systolic deformity and preserved adjacent wall motion—are particularly at risk of sudden death.[25] It has been suggested that because activation of injured muscle is slow, it may still be in electrical diastole when the surrounding muscle is in systole.[26] As the ventricle contracts the injured segment would be stretched and this would induce electrical activation in this area.[27] This electrical wavefront would again propagate slowly to the surrounding normal tissue, which by that time would be no longer refractory and so would be reactivated.

MECHANICALLY INDUCED REENTRY

An important arrhythmogenic mechanism is reentry.[26,28,29] The basic principles underlying the development of a reentry circuit may be illustrated by the following model. A propagating impulse may meet an obstacle—for example, infarcted muscle or scar tissue. The impulse would then divide into two and pass round either side. If conduction around the obstacle is impaired, conduction may fail down one limb (decremental conduction) and be blocked. If the impulse travelling down the other limb is slowed it may reach the distal part of the blocked limb after a delay which has allowed time for the blocked limb to become re-excitable. The impulse may then travel backwards up this limb and then continue round the obstacle in a circular fashion following in the wake of the change in muscle from the refractory to the excitable state. This constitutes a reentry circuit which is autonomous and may take over the activation of the ventricle.

An obstacle does not necessarily need to be an anatomical one: it could be created by an inhomogeneous alteration in the refractoriness in neighbouring fibre groups which may induce "functional" unidirectional block. It is apparent therefore from the above model that factors which create regional differences in conduction and excitability would be expected to encourage the development of reentry. In this context it has been shown that conduction block may be induced by local differences in refractory period of the order of 11–16 ms in atrial tissue[30] and of the order of 10–20 ms in ventricular muscle.[31] The path of a reentry circuit is usually in the border zone between scar tissue (or non-conductive muscle) and normal myocardium. Local mechanical stress has been shown to be magnified by up to four times at the junction between normal myocardium and scar tissue by a process known as stress amplification.[32] This may exaggerate regional electrical inhomogeneity at border zones and this territory would be particularly susceptible to mechanically induced electrophysiological effects.

ABNORMAL CURRENT FLOW

Another possibility is abnormal current flow. Inhomogeneous wall stress or strain, particularly marked in the presence of ischaemia[22-24] could produce local electrical inhomogeneity by contraction-excitation feedback. For example one area could have wall motion that is out of phase with an adjacent area (dyskinesia). The two areas would then generate current by virtue of the potential differences created by the now out of phase action potentials which would stimulate adjacent cells during the period of enhanced excitability.[28]

AFTERDEPOLARISATIONS

Early afterdepolarisations are seen as inflections of the normal repolarisation phase of the action potential.[16,21,31] If such inflections are large enough they can trigger an early beat and they have been implicated in the genesis of arrhythmias. The interpretation of inflections in the downstroke of the monophasic action potential that is characteristic of early afterdepolarisations, however, is contentious because it is impossible to exclude a mechanically induced artefact caused by passive electrical changes at the tissue/electrode interface.[33,34] Nonetheless, several observations support the possibility that these afterdepolarisations are not an artefact.[35,36] Also the monophasic action potential electrode reliably records early afterdepolarisations in vivo under circumstances known to produce them in vitro, when they are recorded by microelectrodes.[37,38]

CELLULAR MECHANISMS

Cellular mechanisms may involve stretch and fibre excursion.[15] Stretch would invoke a nonspecific permeability change perhaps via stretch activated channels[39] and fibre excursion would invoke a change in intracellular calcium.[40] It may be that enhanced excursion deactivates force by reducing the affinity of calcium for troponin C. Calcium comes off the myofilaments and increases sarcoplasmic concentrations to prolong the action potential via electrogenic sodium-calcium exchange[41] or calcium activated currents.[42]

Therapeutic relevance

Electromechanical interactions may be relevant to the high incidence of sudden death caused by ventricular arrhythmia in patients with impaired left ventricular function.[1-5] Such interactions may also be relevant in patients with acute ischaemia, in whom local wall motion abnormality is a usual early feature.[22-24] Several factors may interrelate with electromechanical interaction. For example, arrhythmia may be initiated by an extrasystole or the subsequent beat. Both the extrasystolic and the post extra-systolic impulse have an altered cycle length and are associated with altered force of contraction. In addition these impulses may induce a sudden change in direction of propagation which in turn may alter the orientation of wall stress between areas of normal and ischaemic myocardium or between neighbouring areas of normal and abnormal wall motion.

Therapeutic interventions designed to manipulate preload and afterload are now commonly used, as are drugs that influence the inotropic state of the ventricle. In fact, load reduction, a pure mechanical intervention, may turn out to be an antiarrhythmic intervention in congestive heart failure.[43] An important consideration would be the relative effects of a drug given to alter loading conditions on the adjacent normal and abnormal segment of ventricle. It may be that such a medication would have an antiarrhythmic effect in one area and an arrhythmogenic effect in another area with a different force-tension velocity profile. Understanding of these mechanisms involving electromechanical interaction may be important for the future development of therapeutic strategies.

1 Weaver WD, Lorch GS, Alvarez HA, Cobb LA. Angiographic findings and prognostic indicators in patients resuscitated from cardiac death. *Circulation* 1976;54:895–900.

2 Schultz RA, Strauss HW, Pitt B. Sudden death in the year following myocardial infarction: relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. *Am J Med* 1977;62:192–9.

3 Multicentre Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–6.

4 White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44–51.

5 Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR, Blackbourne BD, Davis JH. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. *Circulation* 1974;49:790–8.

6 Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675–80.

7 Bigger JT. Prevalence and possible mechanisms of ventricular arrhythmias in congestive heart failure. Royal Society of Medicine Services. Round table series. New perspectives in cardiovascular medicine No 4. Arrhythmias in heart failure, new frontiers, 1988:11–27.

8 Califf RM, McKinnis RA, Burks J, *et al*. Prognostic implications of ventricular arrhythmias during 24 hour ambulatory monitoring in patients undergoing cardiac catheterization for coronary artery disease. *Am J Cardiol* 1982;50:23–31.

9 Swerdloe CD, Winkle RA, Mason JW. Determinants of survival in patients with ventricular tachyarrhythmias. *N Engl J Med* 1983;308:1436–42.

10 Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy; observations in 35 patients. *Am J Cardiol* 1983;51:507–12.

11 WHO. Sudden cardiac death. Report of a WHO scientific group. WHO technical report series. 1985:726.

12 Sideris DA. The importance of blood pressure in the emergence of arrhythmias. *Eur Heart J* 1987;8 (Suppl D):129–31.

13 James MA, Jones JV. Ventricular arrhythmia in untreated newly presenting hypertensive patients compared with a matched normal population. *J Hypertens* 1989;7:409–15.

14 Olshausen K, Schwartz F, Appelbach J, Rohrig N, Kramer B, Kubler W. Determinants of the incidence of severity of ventricular arrhythmias in aortic valve disease. *Am J Cardiol* 1983;51:1103–9.

15 Lab MJ. Contraction-excitation feedback in myocardium: physiological basis and clinical relevance. *Circ Res* 1982;50:757–66.

16 Franz MR, Burkhoff D, Yue DT, Sagawa K. Mechanically induced action potential changes and arrhythmia in isolated and in situ canine heart. *Cardiovasc Res* 1989;23:213–23.

17 Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Changes in myocardial repolarisation in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction-excitation feedback in humans. *Circulation* 1988;77:70–7.

18 Taggart P, Sutton PMI, Treasure T, *et al*. Monophasic action potentials at discontinuation of cardiopulmonary bypass: evidence of contraction-excitation feedback in man. *Circulation* 1988;77:1266–75.

19 Dean JW, Lab MJ. Arrhythmia in heart failure: the role of mechanically induced changes in electrophysiology. *Lancet* 1989;i:1309–12.

20 Calkins H, Maughan L, Weisman HF, Sugiura S, Sagawa K, Levine JH. Effects of acute volume load on refractoriness and arrhythmia development in isolated chronically infarcted canine hearts. *Circulation* 1989;79:687–97.

21 Taggart P, Sutton P, John R, Lab M, Swanton H. Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre. *Br Heart J* 1992;67:221–9.

22 Tyberg JV, Forrester JS, Parmley WW. Altered segmental function and compliance in acute myocardial ischemia. *Eur J Cardiol* 1974;1:307–17.

23 Forrester JS, Wyatt HL, da Luz PL, Typerg JV, Diamond GA, Swan HJC. Functional significance of regional ischemic contraction abnormalities. *Circulation* 1976; 54:64–70.

24 Eaton LW, Weiss JL, Bulkey BH, Garrison JB, Weisfeldt ML. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. *N Engl J Med* 1979;300:57–62.

25 Meizlish JL, Berger HJ, Plankey M, Errico D, Levy W, Zaret BL. Functional left ventricular aneurysm formation after acute transmural myocardial infarction. *N Engl J Med* 1984;311:1001–6.

26 Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. *Circ Res* 1964;14:44–60.

27 Hansen DE, Craig CS, Hondeghem LM. Stretch-induced arrhythmias in isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback. *Circulation* 1990;81:1094–105.

28 Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983;67:1356–67.

29 Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989;69:1049–1169.

30 Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia: II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. *Circ Res* 1976; 39:168–77.

31 Gough WB, Mehra R, Restivo M, Zeiler RH, El-Sherif N. Reentrant ventricular arrhythmias in the late myocardial infarction period in the dog: 13 correlation of activation and refractory maps. *Circ Res* 1985;57:432–42.

32 Bogen DK, Rabinowitz SA, Needleman A, McMahon TA, Abelmann WH. An analysis of the mechanical disadvantage of myocardial infarction in the canine left ventricle. *Circ Res* 1980;47:728–41.

33 Hoffman BF, Cranefield PF, Lepeschkin E, Surawicz B, Herlich HC. Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;196:1297–301.

34 Olsson SB, Edvardsson N, Hirsch I, Blomstrom P. Methodological aspects of invasive evaluation of myocardial repolarisation. In: Butrous GS, Schwartz PJ, eds. *Clinical aspects of ventricular repolarisation*. London: Farrand Press, 1989:67–79.

35 Calkins H, Maughan WL, Kass DA, Sagawa K, Levine JH. Electrophysiological effect of volume load in isolated canine hearts. *Am J Physiol* 1989;256:1697–706.

36 Lab MJ. Contribution of mechano-electric coupling to ventricular arrhythmias during reduced perfusion. *Int J Microcirc Clin Exp* 1989;8:433–42.

37 El-Sherif N, Zeiler RH, Craelius W, Gough WB, Henkin R. QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations. Afterdepolarizations and ventricular arrhythmias. *Circ Res* 1988;63:286–305.

38 Levine JH, Spear JF, Guarnieri T, *et al*. Cesium chloride induced long T syndrome: demonstration of afterdepolarizations and triggered activity in vivo. *Circulation* 1985;72:1092–103.

39 Craelius W, Chen V, El-Sherif N. Stretch activated ion channels in ventricular myocytes. *Biosci Rep* 1988;8: 407–14.

40 Lab MJ, Allen DG, Orchard CH. The effects of shortening on myoplasmic calcium concentration and on the action potential in mammalian ventricular muscle. *Circ Res* 1984;55:825–9.

41 Mullins LJ. The generation of electric currents in cardiac fibres by Na/Ca exchange. *Am J Physiol* 1979;236:103–10.

42 Colquhoun D, Neher E, Reuter H, Stevens CF. Inward current channels activated by intracellular calcium in cultured cardiac cells. *Nature* 1981;294:752–4.

43 Webster MWI, Fitzpatrick MA, Nicholls MG, Ikram H, Wells JE. Effect of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol* 1985;56:566–9.

Br Heart J 1992;67:216–20

Clinical and angiographic prediction of cardiac death after coronary artery bypass graft surgery

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Abstract

Objectives—To study the risk factors for cardiac mortality after coronary artery bypass graft surgery.

Design and Setting—Follow up study of patients who had undergone coronary artery bypass graft surgery at the University Hospital of Oulu, Finland.

Patients and Interventions—339 consecutive patients who underwent cardiac catheterisation three months after bypass surgery.

Main Outcome Measures —Incidence of cardiac deaths during the follow up period of five years and predictive value of clinical and angiographic variables for subsequent cardiac mortality.

Results—The incidence of cardiac deaths was 5·1%, and 81% of these were sudden deaths. The postoperative ejection fraction was significantly lower in the patients with subsequent cardiac death than in the survivors ($p < 0{\cdot}001$), and their left ventricular end systolic and end diastolic volumes were higher ($p < 0{\cdot}001$ and $p < 0{\cdot}05$ respectively). The incidence of cardiac deaths was 43% in the patients with a postoperative ejection fraction of <40%. The myocardial jeopardy index after surgery and the rate of graft patency were not significantly different in the survivors and patients who died. The only clinical factors that were different between the groups were postoperative use of diuretics ($p < 0{\cdot}001$) or digitalis ($p = 0{\cdot}02$). After adjustment for other prognostic variables by the proportional hazards method, a low postoperative ejection fraction remained significant as a predictor of the relative risk of cardiac mortality five years after operation ($p < 0{\cdot}01$).

Conclusions—Patients with angiographic evidence of impaired left ventricular function after bypass surgery are still at relatively high risk of dying suddenly, but myocardial ischaemia due to incomplete revascularisation is not strongly associated with an increased risk of cardiac mortality. Conventional clinical methods do not seem to be helpful for identifying patients with an increased risk of cardiac death after bypass surgery.

Many patients with ischaemic heart disease are presently treated by coronary artery bypass graft surgery to improve survival and relieve symptoms. Coronary artery bypass surgery may have beneficial effects on survival in those patients who have signs of impaired left ventricular function or severe coronary artery disease or both in preoperative angiographic studies.[1-3] Revascularisation effectively abolishes myocardial ischaemia and left ventricular function may also be altered after surgery.[4,5] The risk profile for the patients may thus change significantly after bypass operation.

We have prospectively followed up 339 patients in whom clinical and angiographic features had been assessed before and three months after bypass surgery. Our main purpose was to evaluate the postoperative risk factors for subsequent cardiac mortality during the five years after operation. Knowledge of these risk factors could allow new strategies to be developed to improve the survival of patients after revascularisation surgery.

Methods

PATIENTS

The patient population consisted of 339 consecutive patients who were treated by coronary artery bypass graft surgery in our department and who gave their informed consent for recatheterisation at three months after operation. They were subsequently followed up for five years. Eight patients had refused recatheterisation, and were excluded from the consecutive series. Tables 1 and 2 show the preoperative and postoperative clinical features of the patients.

CARDIAC CATHETERISATION AND ANGIOGRAPHIC STUDIES

The preoperative and postoperative selective coronary artery and bypass graft angiograms were performed on multiple projections including caudal and cranial views and were interpreted as described earlier.[6] Luminal narrowings of the coronary arteries or bypass grafts >50% were regarded as significant lesions. Left ventricular volumes were quantified by biplane left ventricular cineangiography.[6] The ejection fraction was calculated by the biplane area-length method.

We used the myocardial jeopardy index to quantify the extent of the myocardium at risk

Table 1 *Preoperative and perioperative data*

Data	*Alive (n=316)*	*Cardiac death (n=17)*
	Clinical data	
Age (mean (SD) yr)	50 (7)	51 (9)
Sex (F/M)	37/279	2/15
NYHA class:		
I	6 (0 to 4%)	1 (0 to 29%)
II	45 (10 to 19%)	1 (0 to 29%)
III	183 (53 to 64%)	6 (14 to 62%)
IV	82 (21 to 31%)	4 (7 to 50%)
Symptoms of CHF	63 (15 to 24%)	4 (7 to 50%)
Previous MI:		
0	156 (45 to 56%)	6 (14 to 62%)
1	114 (31 to 42%)	8 (23 to 72%)
2 Or more	46 (10 to 20%)	3 (4 to 43%)
Medication:		
Digitalis	109 (30 to 41%)	8 (23 to 72%)
Diuretic	86 (22 to 32%)	10 (33 to 82%)*
β Blocking agent	282 (88 to 93%)	13 (50 to 93%)
Calcium antagonist	166 (48 to 59%)	12 (44 to 90%)
Antiarrhythmic drug	12 (2 to 7%)	2 (1 to 36%)
Electrocardiogram:		
Q waves	106 (30 to 41%)	9 (28 to 77%)
Bundle branch block	20 (4 to 10%)	2 (1 to 36%)
LVH	12 (2 to 7%)	1 (0 to 29%)
x Ray film:		
Cardiac enlargement	101 (27 to 38%)	8 (23 to 72%)
Congestion	7 (1 to 5%)	0 (0 to 20%)
	Angiographic data	
Coronary angiogram:		
1 Vessel disease	38 (8 to 16%)	0 (0 to 20%)
2 Vessel disease	97 (25 to 36%)	6 (14 to 62%)
3 Vessel disease	181 (53 to 64%)	11 (38 to 86%)
Left ventriculogram:		
LVEDP (mm Hg)	14 (SD 6) (13 to 15)	20 (SD 6) (17 to 23)**
LVESVI (ml/m^2)	34 (SD 23) (31 to 37)	49 (SD 22) (38 to 60)*
LVEDVI (ml/m^2)	83 (SD 60) (76 to 90)	93 (SD 24) (81 to 105)
LVEF (%)	58 (SD 11) (57 to 59)	49 (SD 13) (42 to 56)*
Contractility score:		
7– 8	236 (71 to 81%)	7 (18 to 67%)
9–11	41 (9 to 17%)	6 (14 to 62%)
12 or more	39 (8 to 16%)	4 (7 to 50%)
	Perioperative data	
No of inserted grafts	3·0 (SD 1·0) (2·9–3·1)	3·3 (SD 0·9) (2·6 to 4·0)
Use of IMA graft	107 (30 to 39%)	2 (1 to 36%)
Q wave infarction	10 (2 to 6%)	2 (1 to 36%)
Other complications	108 (29 to 40%)	8 (23 to 72%)
Aortic cross clamp (min)	84 (SD 25) (81 to 87)	91 (SD 21) (80 to 102)
Maximal creatine kinase MB (U/l)	67 (SD 88) (57 to 77)	79 (SD 66) (45 to 113)

*$p < 0{\cdot}05$; **$p < 0{\cdot}01$.
95% Confidence intervals for the means and frequencies in parenthesis.
CHF, congestive heart failure; MI, myocardial infarction; LVH, left ventricular hypertrophy; LVEDP, left ventricular end diastolic pressure; LVESVI, left ventricular end systolic volume index; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; IMA, internal mammary artery.

of ischaemia after bypass surgery. Anterior myocardial jeopardy was when the stenotic (>50%) left anterior descending coronary artery without a patent bypass graft was supplying a normal or hypokinetic anterior or septal left ventricular wall segements, or both. Inferior jeopardy was present when the stenotic right coronary artery without a patent bypass graft was supplying a normal or hypokinetic ("viable") inferior left ventricular segment; and posterior jeopardy was when the stenotic left circumflex coronary artery without a patent bypass graft was supplying a viable posterior left ventricular segment. The range of the jeopardy index was from 0 (no jeopardy) to 3 (all segments in jeopardy).

The left ventricle was divided into five segments on the right anterior oblique projection (anterobasal, anterolateral, apical, diaphragmatic, and posterobasal), and into two segments on the left anterior oblique projection (posterobasal, septal). Each segment was coded for wall motion as normal (1 point), hypokinetic (2 points), akinetic (3 points), or dyskinetic (4 points). The sum of the points for each segment was used as a scoring system for left ventricular contractility as follows: 7 or 8 points, normal or mild contraction abnormality; 9–11, moderate contraction abnormality; more than 12, severe contraction abnormality.

PERIOPERATIVE DATA

Aortic cross clamping time and maximal creatine kinase MB release into plasma after operation were determined in each patient. Perioperative complications, including low output syndrome, reoperation due to bleeding, electrocardiographic conduction disturbances, atrial fibrillation, and signs of post-pericardiotomy syndrome were also noted. Perioperative myocardial infarction was defined as new occurrence of Q waves in the electrocardiogram.

FOLLOW UP

A questionnaire was sent to all patients. If a complete answer was not received the patients or their relatives or primary physicians were contacted by telephone. The cut off point for

Table 2 Postoperative data

Data	*Alive (n = 316)*	*Cardiac death (n = 17)*
	Clinical data	
NYHA class:		
I	128 (34 to 46%)	2 (1 to 36%)
II	139 (39 to 50%)	12 (44 to 90%)
III	46 (11 to 19%)	1 (1 to 36%)
IV	3 (0 to 3%)	1 (0 to 29%)
Symptoms of CHF	47 (11 to 19%)	6 (14 to 62%)
Medication:		
Digitalis	123 (34 to 45%)	13 (50 to 93%)*
Diuretic	77 (19 to 30%)	13 (50 to 93%)**
β Blocking agent	265 (80 to 88%)	12 (44 to 90%)
Calcium antagonist	63 (15 to 24%)	0 (0 to 20%)
Antiplatelet agent	166 (47 to 59%)	6 (14 to 62%)
Anticoagulant	150 (42 to 53%)	11 (38 to 86%)
Smoking history:		
Non-smoker	77 (19 to 30%)	5 (10 to 56%)
Ex-smoker	189 (55 to 65%)	10 (33 to 82%)
Smoker	50 (11 to 21%)	2 (7 to 50%)
Hypertension	66 (17 to 26%)	4 (7 to 50%)
Diabetes	17 (3 to 8%)	2 (1 to 36%)
Cholesterol (mmol/l)	7·0 (SD 1·4) (6·8–7·2)	6·6 (SD 1·6) (5·8–7·4)
High density lipid cholesterol (mmol/l)	1·0 (SD 0·3) (0·9–1·0)	1·0 (SD 0·2) (0·9–1·1)
Triglycerides (mmol/l)	2·2 (SD 1·4) (2·0–2·4)	2·2 (SD 1·4) (1·5–2·9)
Electrocardiogram:		
Q waves	116 (32 to 42%)	11 (38 to 86%)
Bundle branch block	25 (5 to 11%)	3 (4 to 43%)
LVH	12 (2 to 7%)	1 (0 to 29%)
x Ray:		
Enlarged cardiac size	145 (40 to 51%)	12 (44 to 90%)
Congestion	6 (1 to 4%)	1 (0 to 29%)
	Angiographic data	
Graft patency	79 (SD 26) (76 to 82)	73 (SD 29) (58 to 87)
Jeopardy score:		
0	152 (43 to 51%)	6 (14 to 62%)
1	127 (34 to 46%)	5 (10 to 56%)
2	33 (7 to 15%)	5 (10 to 56%)
3	4 (0 to 3%)	1 (0 to 29%)
Left ventriculogram:		
LVEDP (mm Hg)	14 (SD 5) (13 to 15)	20 (SD 5) (17 to 23)**
LVESVI (ml/m^2)	35 (SD 22) (33 to 37)	65 (SD 38) (45 to 85)**
LVEDVI (ml/m^2)	80 (SD 57) (74 to 86)	102 (SD 42) (80 to 124)
LVEF (%)	58 (SD 12) (57 to 59)	40 (SD 15) (32 to 48)
Contractility score:		
7–8	233 (69 to 79%)	6 (14 to 62%)
9–11	41 (10 to 17%)	5 (10 to 56%)
12 Or more	42 (10 to 17%)	6 (14 to 62%)

*$p < 0·05$; **$p < 0·01$.
Confidence intervals in parenthesis. Abbreviations as in table 1.

the follow up was five years. When the patient died we reviewed the patient records and necropsy data (if available) and questioned witnesses about events preceding the death. Deaths were classified as cardiac or non-cardiac. Cardiac deaths were classified as sudden if the death occurred within one hour of the onset of symptoms and as non-sudden if it occurred more than one hour after the onset.

STATISTICAL ANALYSIS

Differences in data between the survivors and the patients who died from cardiac causes during the follow up were analysed by χ^2 techniques for discrete variables and the two sample *t* test for continuous variables, which were expressed as mean (SD). The proportional hazards method of Cox was used to adjust for covariates of survival. The cut off points for dividing ejection fraction and graft patency into categories were decided before the statistical analyses of the data. Cumulative survival curves were calculated by the Kaplan-Meier method, and the log rank sum test was used to assess the statistical differences between the survival curves. Statistical procedures were carried out with SAS/STAT (SAS Institute Inc, Cary, NC, USA) software.

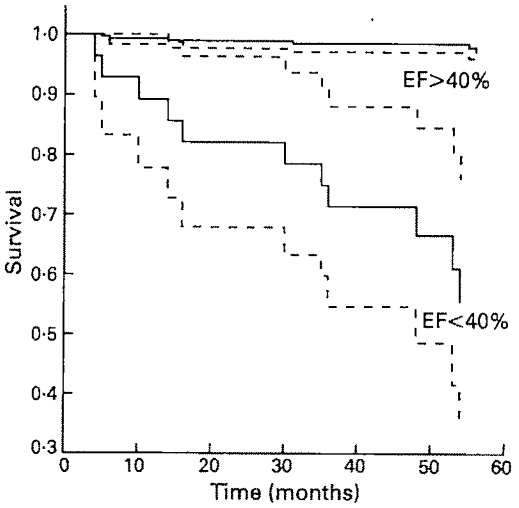
Results

During the follow up there were 17 cardiac deaths (5·1%). Fourteen of these (81%) were sudden deaths and three were non-sudden. Six patients died from non-cardiac causes. Tables 1 and 2 show the preoperative and postoperative clinical and angiographic data of patients who survived and those who suffered cardiac death.

PREOPERATIVE AND PERIOPERATIVE DATA

Preoperative use of diuretic treatment was more common in the patients who died after surgery than in the survivors; but there were no other preoperative clinical features that differed between the groups. Preoperative ejection fraction was lower in the patients who died than in the survivors and abnormalities of left ventricular contraction and increased left ventricular end diastolic pressure were also more common. The preoperative clinical or angiographic severity of coronary artery disease was similar in both groups.

None of the perioperative data differed between the cardiac death patients and survivors. Only two patients with subsequent death had Q wave perioperative myocardial infarction, but new abnormalities in wall motion were detected in five out of 17 patients.



Cumulative survival curves (solid lines) (95% confidence intervals as dotted lines) of the patients with a postoperative ejection fraction (EF) of <40% and those with an EF of >40%. The survival curves were significantly different between the groups at five years after coronary artery bypass surgery ($p < 0·001$).

POSTOPERATIVE DATA

Treatment with digitalis and diuretic drugs was more common three months after surgery in the patients who died than in the survivors. Clinical heart failure tended to be less common in survivors ($p = 0·05$), though the functional class did not differ significantly between the groups (table 2).

Postoperative left ventricular volumes and left ventricular end diastolic pressures were significantly higher and ejection fractions lower in those who died, and abnormalities of left ventricular wall motion were more common. The left ventricular end systolic volume index increased from a mean (SD) of 49 (22) to 65 (38) ml/m^2 ($p < 0·05$) and the ejection fraction decreased from 49 (13) to 40 (15)% ($p < 0·05$) in patients who died of cardiac causes after surgery, whereas left ventricular function remained unchanged in the survivors. The postoperative myocardial jeopardy index did not differ between the groups, nor did the rate of graft patency. Twenty eight patients had an ejection fraction <40% after bypass surgery, and 12 (43%) of these patients died of cardiac causes during the follow up. Only five patients with subsequent cardiac death had a preoperative ejection fraction <40%. Cumulative survival was significantly lower in the patients in whom the postoperative ejection fraction was <40% than in those in whom it was >40% (figure). Eleven (31%) of the patients with a postoperative end systolic volume index >50 ml/m^2 after surgery died from cardiac causes.

After adjustment for prognostic variables by the proportional hazards method, a low postoperative ejection fraction remained significant in predicting the risk of cardiac mortality five years after surgery (table 3).

Table 3 Cox regression analysis and proportional hazard functions

Covariate	*Five year coefficients*	*Standard error of coefficients*	*p Value*
Angiographic:			
Postoperative EF	0·08	0·03	0·001
≥1 occluded graft	0·19	0·53	0·7
Clinical:			
Angina pectoris	0·90	0·82	0·28
Symptoms of CHF	0·15	0·55	0·78
Digitalis usage	0·24	0·69	0·7
Diuretic usage	1·65	0·69	0·02

EF, ejection fraction; CHF, congestive heart failure.

Discussion

The angiographically determined degree of left ventricular dysfunction after coronary artery bypass surgery was most closely associated with an increased risk of cardiac death during the first five years after operation. Although the largest survival benefit from revascularisation has been reported in patients with reduced preoperative ejection fraction,[7-9] the present data show that the risk of cardiac death still remains relatively high in patients with impaired ventricular function after revascularisation. The state of left ventricular function has been identified as the most important risk factor for cardiac mortality in almost all surveys of prognostic indicators in patients with coronary artery disease.[10-14] So far there has been little information, however, on the prognostic importance of left ventricular function assessed after the abolition of ischaemia by revascularisation. The contribution of reversible ischaemic left ventricular dysfunction to a low preoperative ejection fraction in previous studies has been largely unknown, and thus probably accounts for a beneficial effect of revascularisation on survival. Some patients may have continuing myocardial ischaemia which results in abnormalities of wall motion at the time of the preoperative ventriculogram and all abnormalities may not necessarily reflect irreversible scarring of the left ventricle.

Left ventricular function had deteriorated after bypass surgery in many patients who subsequently died. Thus perioperative myocardial damage had occurred in these patients. Perioperative infarction, incomplete revascularisation, acute graft occlusions, technical difficulties leading to long aortic cross clamping times, and inadequate myocardial protection may all give rise to impairment of ventricular function. Perioperative Q wave infarctions were fairly uncommon, but new abnormalities of left ventricular contraction were detected in five of 17 patients who later died. It is obvious that small perioperative infarctions or diffuse myocardial damage often remain undetected after operation. Some institutional factors such as surgical and myocardial preservation techniques may influence the outcome after operation. In any case, the present data emphasise the importance of developments in protection from perioperative myocardial damage, especially with high risk patients in whom left ventricular contractility is impaired before operation.

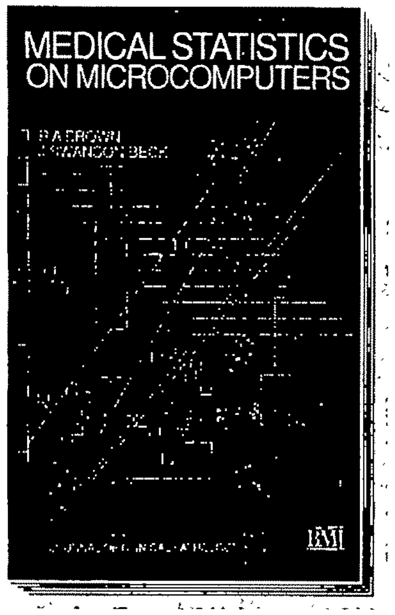
Conventional clinical methods after surgery were not very helpful for identifying patients who would subsequently die of cardiac causes. The functional state of the patients after operation did not reliably identify the increased risk of cardiac death, although those who later died tended to have symptoms of heart failure more often than those who survived. Previous research had indicated that the severity of symptomatic heart failure correlates poorly with the ejection fraction or other indices of left ventricular function.[15 16] Thus impaired left ventricular function may not be easy to recognise clinically despite its adverse prognostic significance. The patients who died were more likely to be taking digitalis and diuretic drugs than those who survived. This association may not be related to the medications themselves, but rather reflects more frequent episodes of past clinical heart failure.

The extent of the myocardium still at jeopardy after revascularisation was not strongly associated with increased cardiac mortality, although the small number of events prevents definite conclusions being reached, the present data suggest that myocardial ischaemia may not be crucial in the initiation of cardiac death during the first years after surgery, when the graft occlusions are infrequent. The common clinical risk factors attached to atherosclerosis, such as smoking, hypertension, and lipid profile, did not distinguish between the survivors and those who died. Atherosclerosis of bypass grafts usually accelerates later than five years after surgery,[15] which perhaps explains the lack of association between the risk factors for atherosclerosis and cardiac death in this series.

Consistent with previous large trials,[1-3] the incidence of cardiac deaths after bypass surgery was relatively low in this study. Despite the small number of patients who died, a high risk subgroup could be identified—namely, those with a low postoperative ejection fraction. Some variables that were not measured here—for example, data from exercise testing, ambulatory monitoring, and signal averaging electrocardiographic and invasive electrophysiological evaluation might give more information about the risk of death after operation. Most of the deaths recorded here were in fact unexpected sudden deaths. It may be that bypass surgery does not abolish the substrate for sustained ventricular tachycardia, which may play an important part in the initiation of fatal events.[17] The extent to which invasive or non-invasive assessment of susceptibility to uncontrollable arrhythmias could further identify a smaller group of very high risk patients within those patients with impaired left ventricular function after bypass surgery remains unknown.

This work was supported in part by the Paavo Nurmi Foundation for Cardiovascular Research, Helsinki, Finland.

1 CASS Principal Investigators and Their Associates. Myocardial infarction and mortality in the Coronary Artery Surgery Study (CASS) randomized trial. *N Engl J Med* 1984;310:750–5.
2 Varnauskas E, and the European Coronary Surgery Study Group. Survival, myocardial infarction, and employment status in a prospective randomized study of coronary bypass surgery. *Circulation* 1985;72(suppl V):V–90-101.
3 Takaro T, Hultgren HN, Lipton MJ, Detre KM, and Participants in the study group. The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. *Circulation* 1976;54(suppl 3):III–107–17.
4 Gersh BJ, Califf RM, Loop FD, Akins CW, Pryor DB, Takaro TC. Coronary bypass surgery in chronic stable angina. *Circulation* 1989;79(suppl I):I–46–59.
5 Braunwald E, Rutherford JD. Reversible ischemic ventricular dysfunction: evidence of hibernating myocardium. *J Am Coll Cardiol* 1986;8:1467–70.
6 Huikuri HV, Korhonen UR, Linnaluoto MK, Takkunen JT. Effect of coronary artery bypass grafting on left ventricular response to isometric exercise. *Am J Cardiol* 1984;54:514–8.
7 Alderman EL, Fisher LD, Litwin P, *et al.* Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;68:785–95.
8 Passamani E, Davis KB, Gillespie MJ, Killip T, and the CASS Principal Investigators and their Associates. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med* 1985;312:1665–79.
9 Pigott JD, Kouchoukos NT, Oberman A, Cutter GR. Late results of surgical and medical therapy for patients with coronary artery disease and depressed left ventricular function. *J Am Coll Cardiol* 1985;5:1036–45.
10 Nelson GR, Cohn PF, Gorlin R. Prognosis in medically treated coronary artery disease. Influence of ejection fraction compared to other parameters. *Circulation* 1975;52:408–12.
11 Moss AJ. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–6.
12 Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. *Circulation* 1979;59:421–9.
13 Massie BM, Conway M. Survival of patients with congestive heart failure: past, present, future prospects. *Circulation* 1987;75(suppl IV):IV11–8.
14 Groudin CM, Rampean L, Thornton JC, Engle JC, Cross FS, Schreiber H. Coronary artery bypass grafting with saphenous vein. *Circulation* 1989;79(suppl I):I–24–9.
15 Franciosa J. Why patients with heart failure die? Hemodynamic and functional determinants of survival. *Circulation* 1987;75(suppl IV):IV–1–3.
16 Weschler AJ, Junod FL. Coronary bypass grafting in patients with chronic congestive heart failure. *Circulation* 1989;79(suppl I):I–52–96.
17 Freeman S, Ruskin JN, Garan H. Effect of myocardial revascularization on inducible ventricular arrhythmias [abstract]. *J Am Coll Cardiol* 1989;13:174A.



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References

1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

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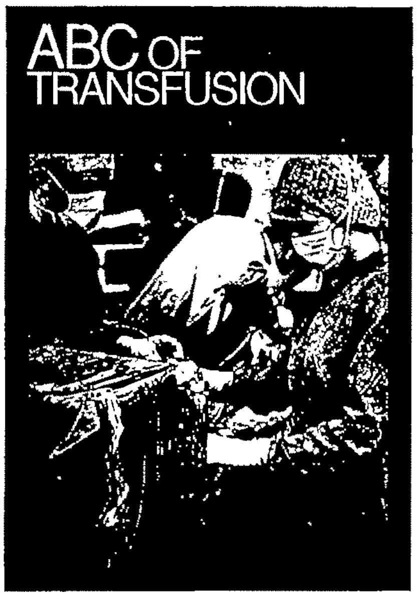

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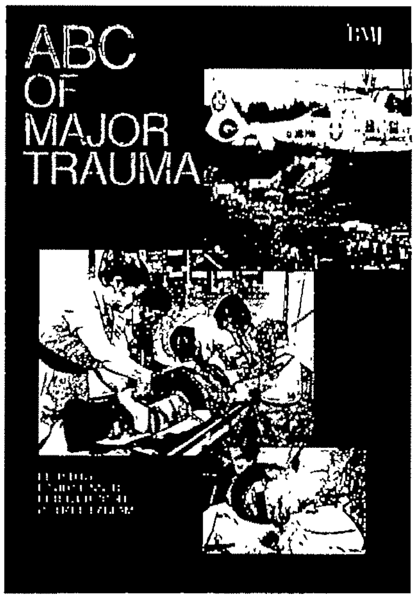

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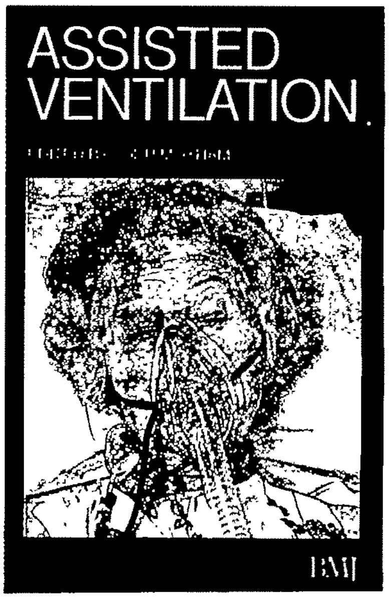

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Br Heart J 1992;67:221–9

Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre

Peter Taggart, Peter Sutton, Roy John, Max Lab, Howard Swanton

Abstract

Objective—**The strong association between ventricular arrhythmia and ventricular dysfunction is unexplained. This study was designed to investigate a mechanism by which a change in ventricular loading could alter the time course of repolarisation and hence refractoriness. A possible mechanism may be a direct effect of an altered pattern of contraction on ventricular repolarisation and hence refractoriness. This relation has been termed contraction-excitation feedback or mechano-electric feedback.**

Methods—**Monophasic action potentials were recorded from the left ventricular endocardium as a measure of the time course of local repolarisation. The Valsalva manoeuvre was used to change ventricular loading by increasing the intrathoracic pressure and impeding venous return, and hence reducing ventricular pressure and volume (ventricular unloading).**

Patients—**23 patients undergoing routine cardiac catheterisation procedures: seven with no angiographic evidence of abnormal wall motion or history of myocardial infarction (normal), five with a history of myocardial infarction but with normal wall motion, and 10 with angiographic evidence of abnormal wall motion—with or without previous infarction. One patient was a transplant recipient and was analysed separately.**

Setting—**Tertiary referral centre for cardiology.**

Results—**In patients with normal ventricles during the unloading phase of the Valsalva manoeuvre (mean (SD)) monophasic action potential duration shortened from 311 (47) ms to 295 (47) ms ($p < 0{\cdot}001$). After release of the forced expiration as venous return was restored the monophasic action potential duration lengthened from 285 (44) ms to 304 (44) ms ($p < 0{\cdot}0001$). In the group with evidence of abnormal wall motion the direction of change of action potential duration during the strain phase was normal in 7/21 observations, abnormal in 6/21, and showed no clear change in 8/21. During the release phase 11/20 observations were normal, five abnormal, and four showed no clear change. In those with myocardial infarction four out of five patients had changes that resembled those with normal ventricles but the changes were less pronounced. There were no differences in any of the three groups between the changes in monophasic action potential duration in patients taking β blockers and those who were not. The changes in monophasic action potential duration in the transplanted heart resembled those in the group with normal ventricles. Inflections on the repolarisation phase of the monophasic action potential consistent with early afterdepolarisations were seen in three of the patients with abnormal wall motion and in none of those with normal wall motion.**

Conclusions—**These results are further evidence that changes in ventricular loading influence repolarisation. When wall motion was abnormal the effects on regional endocardial repolarisation were often opposite in direction to those when it was normal. Thus regional differences in wall motion could generate local electrophysiological inhomogeneity which may be relevant to the association of arrhythmia with impaired left ventricular function.**

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There is a strong association between sudden cardiac death and abnormal ventricular wall motion in patients with coronary artery disease.[1,2] The severity of impairment of left ventricular function is a major predictor of mortality after myocardial infarction[3,4] and patients developing an aneurysm within 48 hours are at particular risk.[5] Death is generally considered to be due to arrhythmia and there is a strong correlation in these patients between abnormal wall motion and ventricular arrhythmia.[6-8] Patients with volume or pressure overload such as aortic valve disease[9-11] or dilated cardiomyopathy[12] commonly have ventricular arrhythmia. Though in some patients with congestive cardiac failure death is due to electromechanical uncoupling, sudden death in these patients is also partly due to the increased incidence of ventricular arrhythmias.[13-15] The explanation for the association between abnormality of ventricular wall motion and serious arrhythmia, however, is unclear.

One possible mechanism may be a direct effect of ventricular loading on the time course of repolarisation and hence refractoriness. This mechanism is known as contraction-excitation feedback[16] (or mechano-electric feedback).

A change in the normal time sequence of repolarisation alters local electrical gradients and is potentially arrhythmogenic.[17] It is known that areas of myocardium where wall motion is abnormal contract differently from normal areas.[18 19] It would be expected therefore that the effect on repolarisation time in abnormally contracting and normally contracting areas of myocardium would be different. In the presence of abnormal wall motion local electrical gradients may be generated which might play a part in the initiation of arrhythmias in these circumstances.

Several studies have examined contraction-excitation feedback in some detail and such feedback has been shown in isolated tissues,[20] isolated hearts,[21-23] and whole animals.[21 24 25] In general these studies have shown that increasing myocardial stretch/strain or increasing loading conditions result in shortening of action potential duration (ie repolarisation time)[16 21] altered refractoriness[22 24 26 27] and arrhythmia formation.[23 25 28 29] Until recently[30-32] there has been no evidence for the existence of this phenomenon in humans. In the present study we used the Valsalva manoeuvre to change ventricular loading within the physiological range in patients undergoing routine cardiac catheterisation for chest pain.[33-35] We recorded monophasic action potentials from the left ventricular endocardium as a measure of repolarisation[36 37] in patients with angiographic evidence of wall motion abnormality and in those without.

The aims of this study were (*a*) to see whether pressure/volume changes influence the timing of regional ventricular endocardial repolarisation and to seek evidence that changes in ventricular loading influence the timing of repolarisation; (*b*) to see whether patients with abnormal wall motion and those with normal wall motion respond differently; (*c*) to see whether there are any electrophysiological changes that would be in keeping with those required for arrhythmia generation.

Patients and methods

We recorded the left ventricular monophasic action potential, arterial pressure, and the routine electrocardiogram in patients undergoing routine cardiac catheterisation for chest pain or, in one patient, routine left ventricular biopsy after heart transplantation.

PATIENTS

Twenty three patients (table 1) were selected at random from the waiting list including one (patient 23) admitted for routine biopsy after a heart transplant. The patients were divided into three groups:

Group 1—Those with no demonstrable angiographic abnormality—that is, normal (n = 7).

Group 2—Those with normal wall motion but a history of myocardial infarction and therefore possible abnormality of left ventricular wall motion not detectable by the methods used in this study (n = 5).

Group 3—Those with angiographic evidence of abnormal left ventricular wall motion either with or without previous history of myocardial infarction (n = 10).

The transplant patient was analysed separately. The study was approved by the hospital ethics committee and informed consent obtained.

METHOD OF EVALUATION OF LEFT VENTRICULAR WALL MOTION FROM LEFT VENTRICULAR CINEANGIOGRAMS

Ventricular synergy was assessed by single plane left ventriculography in the 30° right anterior oblique projection.[38 39] A long axis of the left ventricular endocardial silhouette was drawn between the midpoint of the aortic valve and the left ventricular apex for both end diastolic and end systolic frames. The long axes of the two frames were then aligned and the silhouettes superimposed at the midpoint of the long axis. The long axis was further subdivided to give six segments: anteroapical, inferoapical, anteromedial, inferomedial, anterobasal, and inferobasal. The systolic change in length for each of the above reference segments was normalised for end diastolic length and expressed as percentage shortening (or lengthening in the case of dyskinesis). The inferobasal segment was excluded from analysis of regional contractility because of its large individual variability.[40]

ENDOCARDIAL MONOPHASIC ACTION POTENTIALS

Left ventricular monophasic action potentials were recorded by a purpose built (Cordis) bipolar pressure contact silver/silver chloride catheter electrode (size 7 French). The contact electrode was positioned at the tip with the indifferent electrode 5 mm proximally, flush with the side wall of the catheter. Gentle pressure of the tip electrode against the endocardium gave a signal of between 20 and 40 mV.

ARTERIAL PRESSURE

The routine arterial pressure signal obtained via the catheter sheath was recorded on a Gould Instruments electrostatic chart recorder (model ES1000) at a paper speed of 10 mm/s and used for systolic pressure measurement.

SIGNAL PROCESSING

The monophasic action potential signals were fed into a Gould isolated preamplifier (model 11-5407-58) and then into a DC Gould universal amplifier (model 13-4615-58). The amplifier was set to give an output of 1V for 40 mV input with a frequency response to 300 Hz. The signal was displayed on a Simonsen and Weel monitor (model MTS 102). A Gould Instruments 4 channel RS 3400

Table 1 Details on the 23 patients in the study

										Coronary arteries				
Patient	*Age*	*Sex*	*AP*	*Previous ML*	*LV failure*	*β blockade*	*Calcium antagonists*	*EF*	*No of segments showing abnormal wall motion*	*LAD*	*Cx*	*RCA*	*Group*	*CABG*
1	53	M	+	–	–	–	–	60	0	Severe	Severe	Severe	1	
2	72	M	+	–	–	Atenolol 50 twice a day	Nifedipine 20 twice a day	82	0	Severe	Severe	Severe	1	
3	46	M	–	–	–	–	–	79	0	Mild	Normal	Normal	1	
4	73	M	–	Large anterior	+	–	Diltiazem 60 three times a day	15	3 (2P)	Severe	Severe	Severe	3	
5	48	M	+	Inferior (×2)	–	Metoprolol 50 twice a day	Nifedipine 20 twice a day	66	2	Normal	Severe graft open	Occluded	3	RCA Cx
6	61	M	–	Inferior	–	Atenolol alternate days	–	63	0	Normal	Moderate	Normal	2	
7	52	M	+	–	–	Propranolol 160 once a day	Nifedipine 20 twice a day	80	0	Normal	Normal	Mild	1	
8	52	M	+	–	–	Atenolol 100 once a day	Diltiazem 60 twice a day	79	0	Occluded OM	Normal	Severe	1	
9	61	M	*	–	–	–	–	83	0	Normal	Normal	Normal	1	
10	51	M	+	Lateral	–	Atenolol 50 twice a day	Nifedipine 10 twice a day	84	0	Moderate	Moderate	Moderate	2	
11	56	M	+	Lateral	–	Atenolol 50 once a day	–	46	1	Mild	Normal	Severe	3	
12	53	M	–	Inferior	–	Atenolol 50 once a day	–	54	2	Mild	Moderate	Mild	3	
13	57	M	+	Inferior apex lateral	+	–	Nifedipine 10 three times a day	59	2 (1P)	Moderate	Normal	Moderate	3	
14	49	F	*	–	–	–	–	68	0	Normal	Normal	Normal	1	
15	59	M	+	+	–	Atenolol 50 once a day	–	75	0	Normal	Normal	Normal	2	
16	58	M	+	+	–	–	Nifedipine 20 twice a day	64	1	Occluded	Normal	Ectatic	3	
17	48	M	+	+	–	Metoprolol 50 twice a day	Diltiazem 60 three times a day	80	1	Occluded graft open	Occluded graft open	Moderate	3	Cx LAD
18	59	F	+	+	–	–	Nifedipine 20 three times a day	25	4	Severe	Severe	Tight mid	3	
19	65	M	+	+	+	Atenolol 100 once a day	Nifedipine 20 three times a day	32	2	Occluded graft open	Occluded graft open	Occluded graft open	3	Cx LAD RCA
20	49	M	+	+	–	Atenolol 50 once a day	Nifedipine 20 twice a day	76	0	Moderate	Moderate	Moderate	2	
21	52	F	+	Anteroseptal	–	Propranolol 160 one a day	Diltiazem 60 three times a day	58	2	Mild	Normal	Severe	3	
22	33	M	–	+	–	–	–	78	0	Severe	Normal	Moderate	2†	
23	52	M	–	–	–	–	Nifedipine 20 twice a day							

*Non-specific chest pain; †cardiac transplant.
AP, angina pectoris; MI, myocardial infarction; LV, left ventricle; EF, ejection fraction; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; CABG, coronary artery bypass graft; P, paradoxical motion; OM, obtuse marginal.

chart recorder (model 30-V8404-10) was used for hard copy recordings at a paper speed of 125 mm/s. Hard copy recordings of the routine blood pressure were also recorded in order to synchronise the blood pressure measurements with the monophasic action potentials on a beat to beat basis. The routine electrocardiogram monitored at the time was also recorded. The monophasic action potential recording was calibrated with a direct current millivolt source (Time Electronics model 4045). The blood pressure was calibrated against known pressures of 0 and 100 mm Hg.

PROCEDURE

Routine coronary angiography, via the right femoral artery by the Judkins technique, was performed on all patients (except patient number 23). Left ventricular angiography was performed in the right anterior oblique position. Patient 23 had a left ventricular biopsy only (no coronary angiography or left ventricular angiography).

On completion of the routine procedure the angiography catheter (or biopsy catheter) was replaced with the monophasic action potential catheter which was positioned against the left ventricular wall. Right atrial pacing was established via the right femoral vein at a rate of approximately 15% above the patient's resting heart rate. Two patients (2 and 3) were unpaced but were included because the heart rate from control to phase IIA and from phase III to IVA did not change by more than 1%.

VALSALVA MANOEUVRE

The apparatus used for the Valsalva manoeuvre consisted of a 20 ml syringe for a mouthpiece (plunger removed) attached via rubber tubing to a sphygmomanometer. The size of the syringe ensured a tight seal between the patient's lips and the barrel of the syringe. The patient was asked to blow hard and maintain the mercury column at 40 mm Hg for 15 seconds.

A run-in period of atrial pacing for two minutes established a steady state after which continuous recordings were made during the Valsalva manoeuvre. When feasible the procedure was repeated for up to three times. There was a rest period of three minutes between procedures during which atrial pacing was maintained.

ANALYSIS OF DATA

Monophasic action potential duration was measured at 90% and 70% repolarisation. The terminal portion of the action potential was defined by drawing a tangent to the fastest part of the downstroke to the baseline.[41 42] This

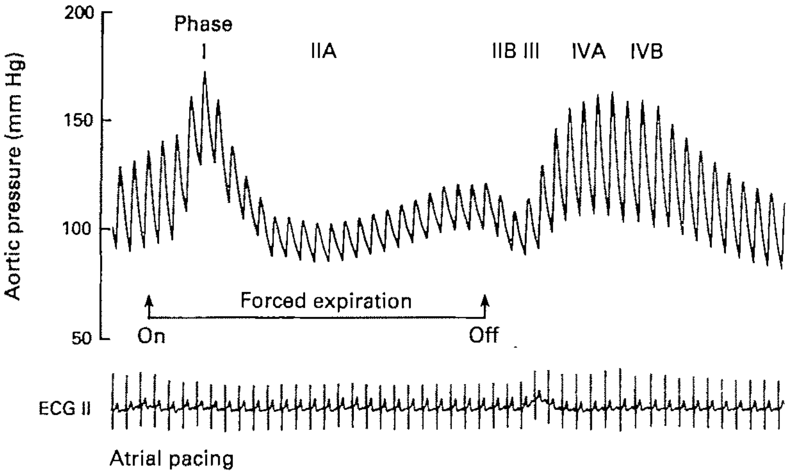


Figure 1 Typical recording of aortic blood pressure during the Valsalva manoeuvre together with the routine electrocardiogram. The four phases of the Valsalva manoeuvre and duration of the forced expiration are shown. Cycle length = 670 ms.

method eliminated the possibility of including afterdepolarisations in the measurements which would have produced long duration action potentials. In addition this technique of measurement also overcomes possible difficulties in measuring action potentials exhibiting a continuous decline of phase IV. Mean values with standard deviations are presented. The data were assessed by a repeated measures analysis of variance and planned comparison of means (Anova).

Results

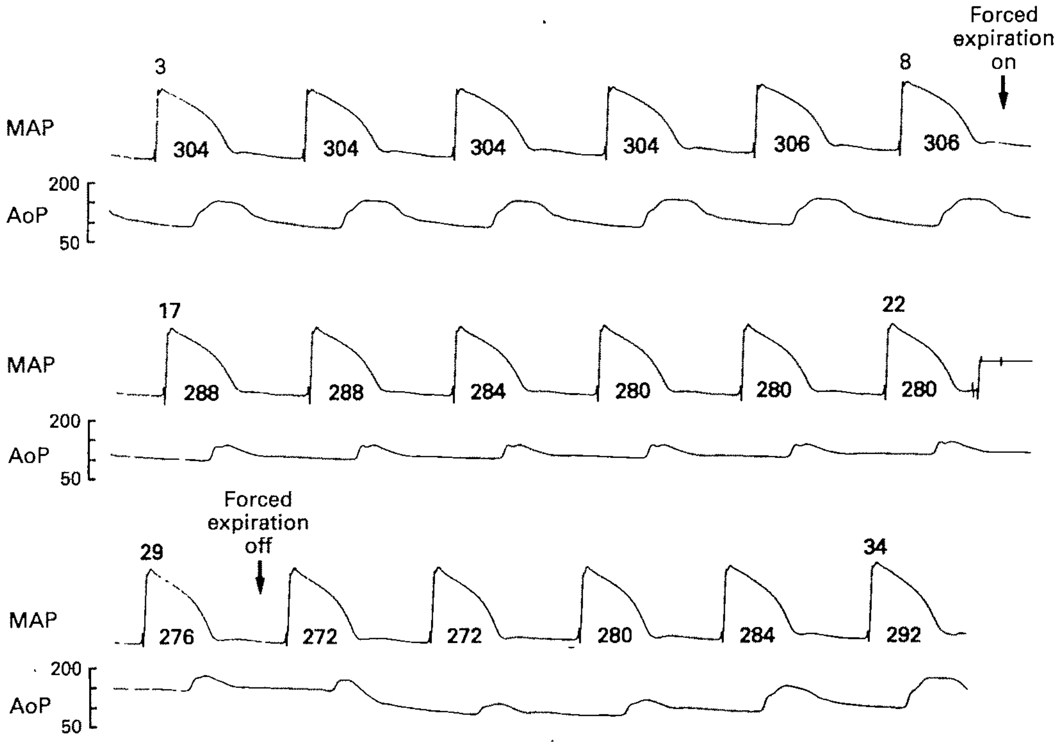
Figure 1 shows a typical blood pressure response to the Valsalva manoeuvre we obtain in our catheter laboratory. The patient takes a deep breath in and then blows hard against a calibrated resistance of 40 mm Hg. This increases the intrathoracic and intraabdominal pressures thereby impeding venous return, reducing ventricular filling, and reducing left ventricular systolic pressure and volume. Four phases are described. The initial increase in blood pressure seen in phase I lasts for a few beats only and is due to a direct effect of the increased intrathoracic pressure, possibly together with an increased preload caused by a shift of blood from the pulmonary bed into the left ventricle. During phase II there is an initial fall in blood pressure (phase IIA) because venous return is impeded. This results in a reflex increase in peripheral resistance and inotropic state of the myocardium curtailing the fall in blood pressure and resulting in a plateau and even a small subsequent rise (phase IIB). After release of the forced expiration intrathoracic pressure returns to normal and refilling of the pulmonary vascular bed results in a transient further fall in blood pressure caused by a further reduction in ventricular filling for about 2–3 beats (phase III). As the venous return is restored and ventricular filling increases the blood pressure rises (phase IV). Reflex autonomic effects may cause an "overshoot" above control levels of blood pressure (phase IVB).

During the Valsalva manoeuvre there were considerable changes in the time course of repolarisation in the recordings of endocardial monophasic action potential coincident with the changes in blood pressure.

Figure 2 shows the changes typical of monophasic action potential in a patient with no angiographic evidence of abnormal wall motion (group 1). During the strain phase (B) the monophasic action potential duration shortened and subsequently increased after release (C). Action potential duration was measured at 90% repolarisation.

In group 3 (those with regional wall abnormalities) there were 21 observations during the strain phase and 20 during the release phase. During the strain phase the direction of change

Figure 2 Tracing of monophasic action potentials and aortic pressure before the Valsalva manoeuvre (beats 3–8) during the strain phase (phase II; beats 17–22), and from the release of forced expiration (phase III) (after beat 29 to beat 34). Zero calibration for the monophasic action potentials is shown at the end of the second panel. Cycle length = 584 ms. (Group 1 patient)



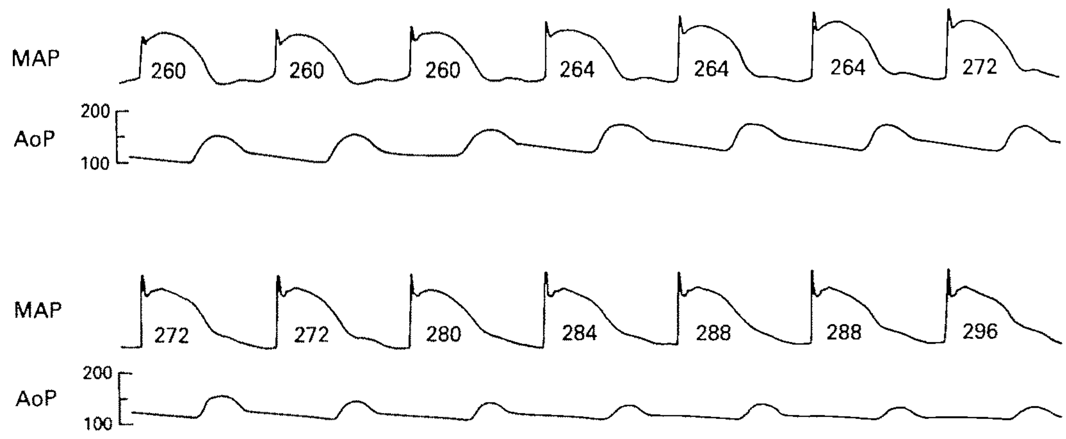


Figure 3 Continuous recording of monophasic action potential and aortic pressure during the strain phase of the Valsalva manoeuvre in a patient with abnormal wall motion and a history of myocardial infarction (group 3). Monophasic action potential duration (at 90% repolarisation) increased progressively from 260 ms to 296 ms as peak systolic pressure fell. The fast phase of repolarisation became progressively delayed possibly representing early afterdepolarisations. Cycle length = 496 ms.

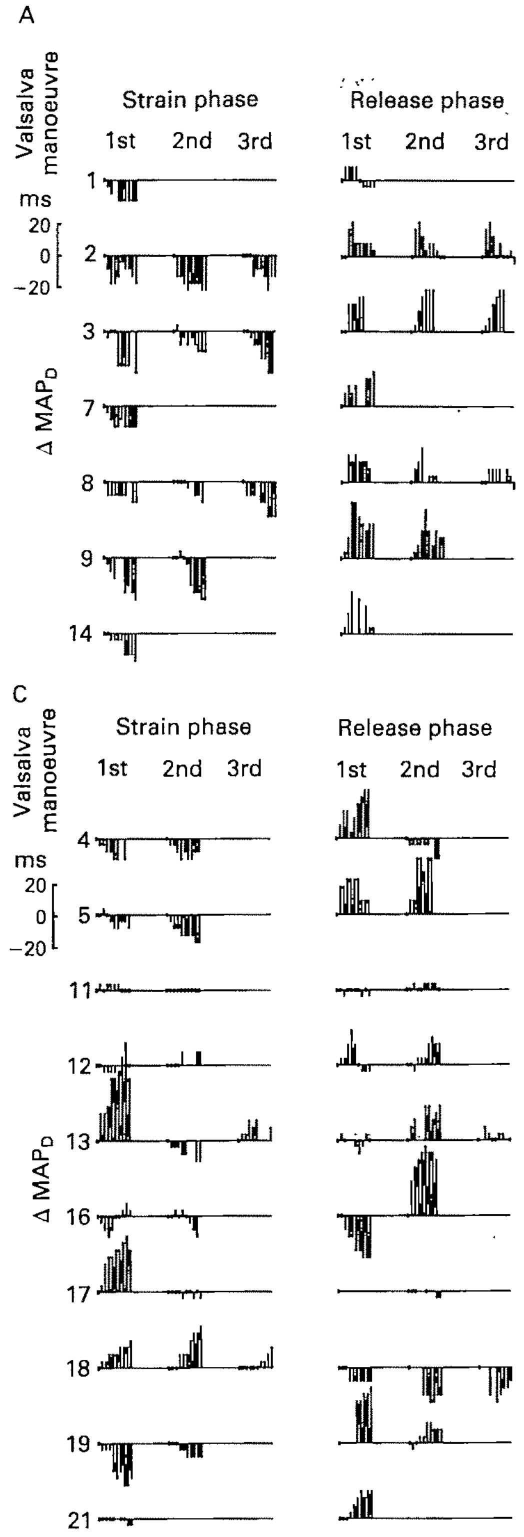
of action potential duration was normal in seven observations, abnormal in six, and showed no clear change in eight. During the release phase 11 were normal, five abnormal, and four showed no clear change. Figure 3 shows an example of changes in monophasic action potential duration which were opposite in direction. Action potential duration increased as systolic pressure fell during the strain phase. In addition the late phase of repolarisation became progressively delayed; this may have represented an afterdepolarisation.

Figure 4 shows the changes in monophasic action potential duration for the first nine beats of the strain phase and the release phase for each patient. Each patient performed up to three Valsalva manoeuvres. The vertical bars indicate the change in monophasic action potential duration with respect to the action potential duration at the start of each phase. As indicated by the scale a bar below the baseline represents a shortening whereas a bar above represents a lengthening. In group 1 there was uniform shortening in the strain phase and uniform lengthening during the release phase. In group 3 this symmetry was no longer apparent with many patients showing changes in the opposite directions to those in group 1. Changes in the opposite direction in at least one

Table 2 Monophasic action potential duration (ms) (mean (SD)) at 90% repolarisation at 70% repolarisation and peak systolic pressure (mmHg) at phases I, IIA, III, IVA and IVB of the Valsalva manoeuvre for patients with no abnormal wall motion and no history of previous myocardial infarction (group 1), those with previous history of myocardial infarction but normal wall motion (group 2), patients with abnormal wall motion (group 3), and for all three groups.

	Strain phase			*Release phase*	
	I	*IIA*	*III*	*IVA*	*IVB*
			At 90% repolarisation		
Group 1	311 (47) $\xrightarrow[n = 14]{0{\cdot}001}$	295 (47)	285 (44) $\xrightarrow[n = 14]{0{\cdot}0001}$	304 (44) 305 (50) $\xrightarrow[n = 11]{0{\cdot}001}$	293 (48)
Group 2	274 (29) $\xrightarrow[n = 9]{NS}$	269 (27)	265 (27) $\xrightarrow[n = 8]{NS}$	271 (29) 270 (30) $\xrightarrow[n = 7]{0{\cdot}005}$	277 (31)
Group 3	285 (33) $\xrightarrow[n = 21]{NS}$	287 (28)	279 (30) $\xrightarrow[n = 20]{NS}$	285 (35) 280 (35) $\xrightarrow[n = 15]{NS}$	278 (34)
Groups 1, 2 and 3	291 (39) $\xrightarrow[n = 44]{0{\cdot}02}$	286 (36)	279 (35) $\xrightarrow[n = 42]{0{\cdot}001}$	289 (38) 286 (41) $\xrightarrow[n = 33]{NS}$	283 (38)
			At 70% repolarisation		
Group 1	282 (47) $\xrightarrow[n = 14]{0{\cdot}001}$	268 (48)	259 (46) $\xrightarrow[n = 14]{0{\cdot}0001}$	271 (43) 271 (49) $\xrightarrow[n = 11]{0{\cdot}015}$	262 (47)
Group 2	249 (30) $\xrightarrow[n = 9]{0{\cdot}002}$	239 (29)	234 (28) $\xrightarrow[n = 8]{0{\cdot}05}$	242 (27) 241 (29) $\xrightarrow[n = 7]{0{\cdot}009}$	250 (31)
Group 3	257 (32) $\xrightarrow[n = 21]{NS}$	256 (26)	249 (21) $\xrightarrow[n = 20]{0{\cdot}015}$	257 (37) 247 (29) $\xrightarrow[n = 15]{NS}$	246 (29)
Groups 1, 2 and 3	263 (39) $\xrightarrow[n = 44]{0{\cdot}0001}$	256 (36)	249 (34) $\xrightarrow[n = 42]{0{\cdot}0001}$	250 (36) 254 (38) $\xrightarrow[n = 33]{NS}$	252 (36)
			Peak systolic pressure (mm Hg)		
Group 1	138 (31) $\xrightarrow[n = 14]{0{\cdot}02}$	97 (37)	66 (26) $\xrightarrow[n = 14]{0{\cdot}0001}$	109 (32) 108 (36) $\xrightarrow[n = 11]{0{\cdot}001}$	145 (33)
Group 2	167 (23) $\xrightarrow[n = 9]{0{\cdot}039}$	110 (19)	86 (15) $\xrightarrow[n = 8]{0{\cdot}0001}$	134 (18) 138 (15) $\xrightarrow[n = 7]{0{\cdot}001}$	174 (22)
Group 3	160 (17) $\xrightarrow[n = 21]{0{\cdot}0001}$	127 (25)	107 (32) $\xrightarrow[n = 20]{0{\cdot}0001}$	135 (35) 130 (23) $\xrightarrow[n = 14]{0{\cdot}0001}$	170 (27)
Groups 1, 2 and 3	155 (25) $\xrightarrow[n = 44]{0{\cdot}0001}$	114 (31)	89 (33) $\xrightarrow[n = 42]{0{\cdot}001}$	126 (29) 124 (29) $\xrightarrow[n = 32]{0{\cdot}0001}$	162 (30)

The significance of any change and the number of observations in each group are shown. NS = not significant at the 95% level.



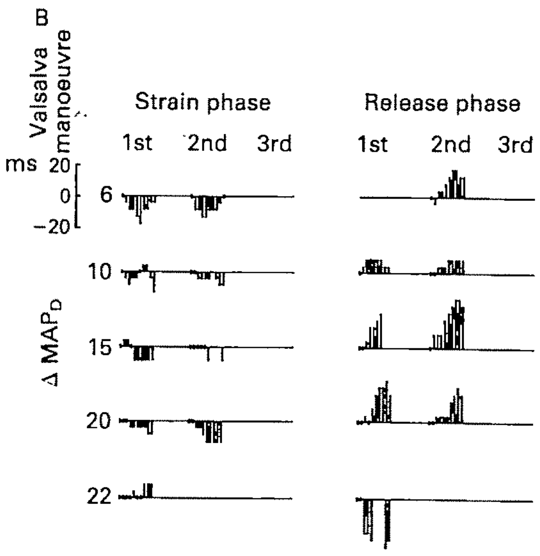


Figure 4 Changes in monophasic action potential duration at 90% repolarisation (MAP_D) during the first nine beats of the strain phase of the Valsalva manoeuvre (from phase I) and during the first four beats after release (from phase III). Between one and three consecutive Valsalva manoeuvres were monitored in patients each from a different site. (A) Patients with no history of myocardial infarction and no angiographic evidence of abnormal wall motion, (B) patients with a history of myocardial infarction but no angiographic evidence of abnormal wall motion, (C) patients with abnormal wall motion either with or without a history of myocardial infarction. The first point (0) in each histogram in each phase is the starting point and subsequent values are the change in milliseconds. Some bars are missing and the bars in patient 13 overlap those in patient 12.

of the manoeuvres was seen in six of the patients. In particular, some patients (for example, case 16) occasionally showed changes in the opposite direction during consecutive Valsalva manoeuvres with the recording electrode positioned at adjacent sites. In group 2 patients in general the changes resembled those in group 1 but were not always as clear cut.

Table 2 shows the mean values. Group 1 patients showed highly significant changes in action potential duration in both phases, reflecting the uniform direction of change in all patients. The lack of uniformity seen in group 3 patients is reflected in the seemingly smaller changes in the mean values particularly at 90% repolarisation. The changes in mean values for group 2 patients in general followed the pattern seen in group 1.

The possible presence of afterdepolarisations seen in fig 3 was also seen in two other patients and an example is shown in fig 5. Figure 5 again represents the progressive development of "afterdepolarisations" in another patient from this group which culminates in a ventricular extrasystole.

We compared the changes in monophasic action potential duration for each of the phases of the Valsalva manoeuvre in patients taking β blockers with those who were not. The only significant difference was during phase IIA in patients in group 1 ($p < 0·03$) and combined groups 1 and 2 ($p < 0·04$)—that is, all patients without abnormal wall motion.

We studied one additional patient who had received a donor heart six months previously. The changes in monophasic action potential duration in this patient were not included in the statistical analysis. However, monophasic action potential duration changed in a manner similar to those in group 1. Two Valsalva manoeuvres were recorded. The aortic pressure record was almost identical for both runs. In figure 6 the aortic pressure tracing is shown together with beat by beat changes in monophasic action potential duration at 90% and 70% repolarisation for the strain phase (from run one) and the release phase (from run two). Figure 7 shows the monophasic action

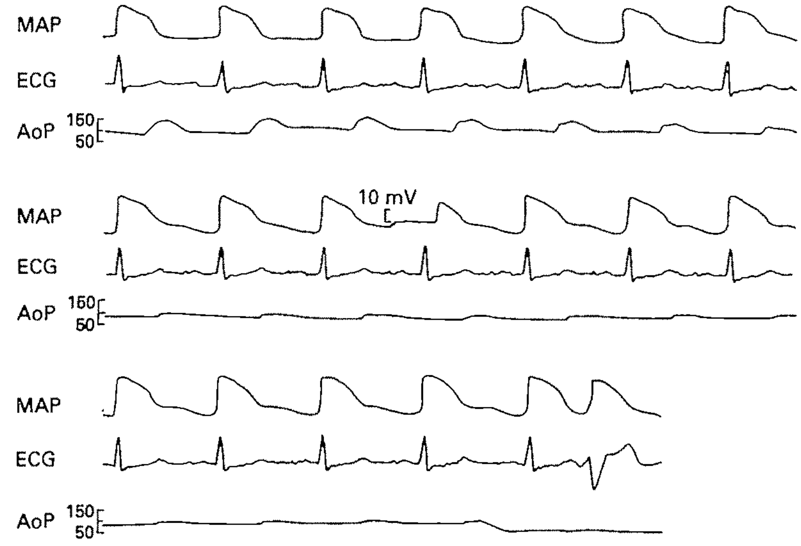


Figure 5 Continuous tracings of monophasic action potential, aortic pressure recording, and electrocardiogram (lead II) during phase II of the Valsalva manoeuvre in a patient with abnormal wall motion and a history of myocardial infarction. The fast phase of repolarisation became progressively delayed culminating in a ventricular extrasystole (arrow). Zero calibration for the monophasic action potential is included between the third and fourth beats in the middle panel. Cycle length = 664 ms.

potentials during the early strain phase. During this strain phase the monophasic action potential duration shortened progressively as aortic pressure fell.

Discussion

Abnormal left ventricular wall motion is a major predictor of sudden cardiac death[1,2] that is often considered to be the result of arrhythmia.[6-8] The mechanism for this relation remains undefined. We examined the effect of acute ventricular pressure/volume changes on ventricular repolarisation in patients with normal and with abnormal wall motion to see whether there were any electrophysiological changes that would be in keeping with those required for arrhythmia formation. A convenient means of altering ventricular pressure/volume is the Valsalva manoeuvre in which a forced expiration impedes venous return, causing a reduction of left ventricular pressure/volume.[33-35] We recorded monophasic action potentials from the left ventricular endocardium as a measure of the time course of repolarisation. We found significant changes in the timing of regional ventricular repolarisation during the Valsalva manoeuvre. In some patients with abnormal wall motion the effects on ventricular repolarisation were opposite in direction to those found in patients with normal wall motion. In both groups of patients the change in the duration of repolarisation in response to changes in ventricular loading suggests that the mechanical effects of the loading may play a part in these changes. It may be argued that the autonomic influences associated with the Valsalva manoeuvre[33-35] may also contribute to our findings because increased sympathetic activity may influence the timing of repolarisation[43-45] (that is, action potential duration). We consider that this contribution is minimal because we confirmed our observations on ventricular unloading to the first few beats—before significant autonomic effects occur.[46] Our observations during ventricular loading were confined to a four beat train during which time changes in autonomic tone would be small. In addition the changes in action potential duration in the transplanted heart, which is devoid of innervation, were comparable in direction to those in our normal patients (group 1). Finally there was no difference in the response in patients receiving β blockade compared with those who were not.

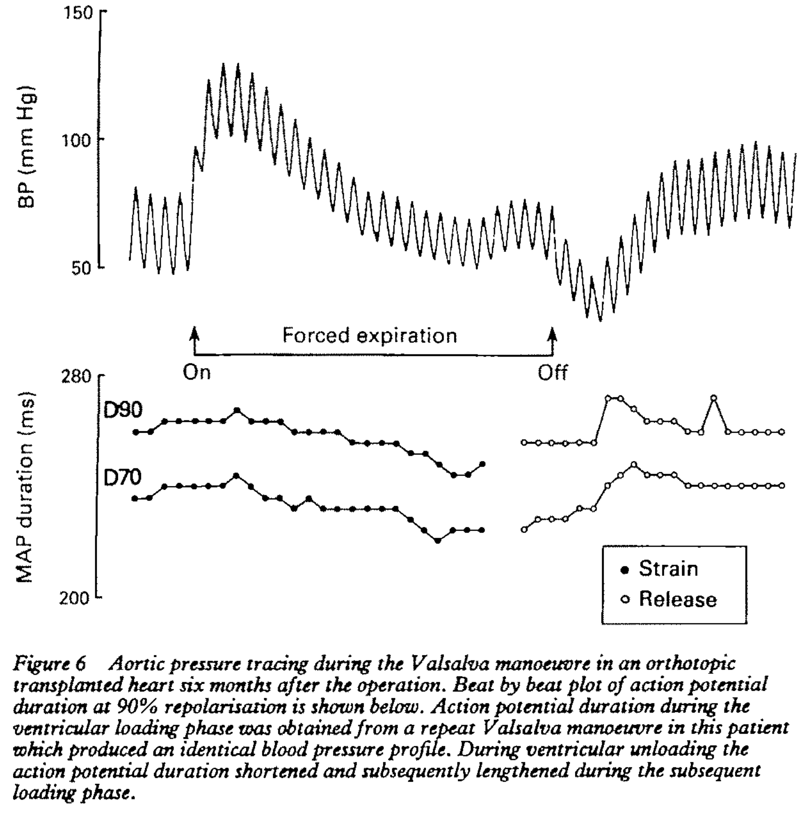


Figure 6 Aortic pressure tracing during the Valsalva manoeuvre in an orthotopic transplanted heart six months after the operation. Beat by beat plot of action potential duration at 90% repolarisation is shown below. Action potential duration during the ventricular loading phase was obtained from a repeat Valsalva manoeuvre in this patient which produced an identical blood pressure profile. During ventricular unloading the action potential duration shortened and subsequently lengthened during the subsequent loading phase.

If we accept that the effects that we have seen are mechanical—in that the changes in ventricular loading directly influence the timing of repolarisation—then our results would be consistent with contraction-excitation feedback. Such a mechanism has been demonstrated experimentally in isolated tissues and in animals. In general, it has been shown that increasing the length of cardiac muscle shortens the action potential duration and decreasing the length of the muscle lengthens the action potential duration.[16] Our patients with normal wall motion (group 1), however, showed opposite effects. A reduction left ventricular volume and peak systolic pressure shortened the monophasic action potential duration and an increase in left ventricular volume and peak systolic pressure lengthened it.

It is probable that several mechanisms are involved—such as stretch and fibre excursion. It has been shown that there is a relation between the extent to which a muscle is allowed to shorten and the duration of the action potential. For example when a contracting muscle is prevented from shortening (that is, isometric contraction) the action potential duration is abbreviated. In the unloading phase

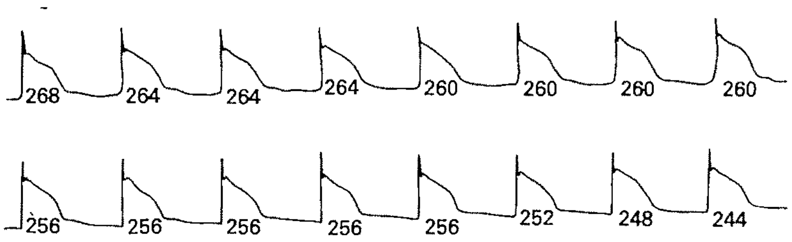


Figure 7 A continuous recording of monophasic action potentials during the strain phase in the patient in figure 7. Monophasic action potential duration is shown at 90% repolarisation and shortened progressively from 268 ms to 244 ms. Cycle length = 584 ms.

of the Valsalva manoeuvre the ventricular cavity size and stroke volume decrease and fibre excursion between end systolic and end diastolic phases is reduced. This would accord with the fibre excursion mechanism being predominant. It is to be expected that fibre excursion would be different in areas of normal and abnormal wall motion. Paradoxical movement (that is, systolic bulging) is common during the early phase of ischaemia when type 1A arrhythmias are common.[47] Local differences in repolarisation and excitability induced by a mechanism such as we describe would facilitate arrhythmia by re-entry mechanisms.

Another mechanism for arrhythmia formation may be the result of early afterdepolarisations[48] that reach threshold for the initiation of a subsequent action potential. An early afterdepolarisation is an inflection on the downstroke of the action potential and can appear in the electrocardiogram as the U wave. Early afterdepolarisations in monophasic action potential recordings could be a mechanical artefact rather than a real electrophysiological phenomenon. Artefacts cannot entirely be ruled out but several studies support the possibility that these are real afterdepolarisations.[25] One preliminary study suggests that mechanically induced early afterdepolarisations in the monophasic action potential show a rate dependence analogous to that of afterdepolarisations recorded with microelectrodes.[49] It may be important that in our study they were accompanied by extrasystoles. These could be attributed to local irritation by the stiff catheter, but extrasystoles have also been seen by various recording techniques in several experimental preparations.[16 20 21 25] We saw some considerable early afterdepolarisations (figs 3 and 5) which were particularly obvious in patients with abnormal wall motion. In the example shown in fig 5 the progressive increase in afterdepolarisations culminated in an extrasystole. In some instances we saw a continuous decline in phase IV even after the termination of the possible afterpotential was seen. We cannot say whether these were artefacts or real phenomena.

There was a wide variability in the size of the effect on action potential duration, which varied from 20 ms to 40 ms in some patients (fig 4). This is greater than the dispersion necessary to facilitate reentrant arrhythmias[50 51] and not dissimilar to action potential durations induced by antiarrhythmic drugs with class III action.[52] In our experience only slight changes in action potential duration were caused by spontaneous variability. Prematurity shortens action potential duration, which depends on the rate and preceding cycle length. For example, during a steady state heart rate of 80/minute (cycle length 750 ms) an early beat of 350 ms shortened the action potential by about 11 ms.[53]

Arrhythmia in patients with coronary heart disease and congestive heart failure is probably multifactorial,[15] with deaths in some instances being due to electromechanical dissociation. In addition to contraction-excitation feedback (or mechano-electric coupling) other important factors may be myocardial fibrosis and hypertrophy[54] activation of the sympathetic nervous system or hypokalaemia induced by a renin angiotensin system[55] diuretic,[56] together with the arrhythmogenic effect of drug treatment such as digoxin and some antiarrhythmic agents. Studies of an animal model of doxorubicin induced heart failure suggest an inherent mechanism not related to mechanical or any of the above effects.[57] Our results, however, support the possibility that mechanically induced electrophysiological changes could play a part in these clinical situations.[58]

Our study confirms that potentially arrhythmogenic changes in action potential duration and excitability in humans may be produced by load changes that are within physiological ranges[59] and that changes in ventricular loading change the time course of repolarisation. An important finding was that such changes could be in opposite directions in patients with normal wall motion and patients with abnormal wall motion. These data suggest that the presence of abnormal wall motion may induce electrophysiological changes by contraction-excitation feedback and this may provide a link between the unexplained association between arrhythmia and impaired left ventricular function.

This study was supported by a grant from the British Heart Foundation.

1 Weaver WD, Lorch GS, Alvarez HA, Cobb LA. Angiographic findings and prognostic indicators in patients resuscitated from cardiac death. *Circulation* 1976;54:895–900.
2 Schultz RA, Strauss HW, Pitt B. Sudden death in the year following myocardial infarction: relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. *Am J Med* 1977;62:192–9.
3 Multicentre Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–6.
4 White HD, Norris RN, Brown MA, Brandt PW, Whitlock RML, Wild CJ. Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44–51.
5 Meizlish JL, Berger HJ, Plankey M, Errico D, Levy W, Zaret BL. Functional left ventricular aneurysm formation after acute transmural myocardial infarction. *N Engl J Med* 1984;311:1001–6.
6 Calvert A, Lown B, Gorlin R. Ventricular premature beats and anatomically defined coronary heart disease. *Am J Cardiol* 1977;39:627–34.
7 Califf RM, Burks JM, Behar VS, Margolis JR, Wagner GS. Relationships among ventricular arrhythmias, coronary artery disease and angiographic and electrocardiographic indicators of myocardial fibrosis. *Circulation* 1978;57:725–32.
8 Califf RM, Mckinnis RA, Burks J, *et al.* Prognostic implications of ventricular arrhythmias during 24 hour ambulatory monitoring in patients undergoing cardiac catheterization for coronary artery disease. *Am J Cardiol* 1982;50:23–31.

9 Santinga JT, Kirsh MM, Brady TJ, Thrall J, Pitt B. Left ventricular function in patients with ventricular arrhythmias and aortic valve disease. *Ann Thorac Surg* 1983;35:152–5.

10 Klein RC. Ventricular arrhythmias in aortic valve disease: analysis of 102 patients. *Am J Cardiol* 1984;53:1079–83.

11 Kostis JB, Tupper B, Moreyra AE, Hosler M, Cosgrove N, Terrigino C. Aortic valve replacement in patients with aortic stenosis. Effect on cardiac arrhythmias. *Chest* 1984;85:211–4.

12 Swerdlow CD, Winkle RA, Mason JW. Determinants of survival in patients with tachyarrhythmias. *N Engl J Med* 1983;308:1436–42.

13 Wilson JR, Schwartz JS, Sutton MS, *et al.* Prognosis in severe heart failure. Relation to haemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403–10.

14 Holmes J, Kubo SH, Cody RJ, Klingfield P. Arrhythmias in ischaemic and non-ischaemic dilated cardiomyopathy: prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985;55:146–51.

15 Dargie HJ, Cleland JFG, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987;75:98–107.

16 Lab MJ. Contraction-excitation feedback in myocardium: physiological basis and clinical relevance. *Circ Res* 1982;50:757–66.

17 Janse MJ, Kleber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. *Circ Res* 1981;49:1069–81.

18 Tyberg JV, Forrester JS, Parmley WW. Altered segmental function and compliance in acute myocardial ischemia. *Eur J Cardiol* 1974;1:307–17.

19 Forrester JS, Wyatt HL, da Luz PL, Typerg JV, Diamond GA, Swan HJC. Functional significance of regional ischemic contraction abnormalities. *Circulation* 1976;54:64–70.

20 Kaufmann RL, Lab MJ, Hennekes R, Krause H. Feedback interaction of mechanical and electrical events in the isolated mammalian ventricular myocardium (cat papillary muscle) *Pflugers Arch* 1971;324:100–23.

21 Franz MR, Burkhoff D, Yue DT, Sagawa K. Mechanically induced action potential changes and arrhythmia in isolated and in situ canine heart. *Cardiovasc Res* 1989;23:213–23.

22 Lerman BB, Burkhoff D, Yue DT, Sagawa K. Mechanoelectrical feedback. Independent role of preload and contractility in modulation of canine ventricular excitability. *J Clin Invest* 1985;76:1843–50.

23 Calkins H, Maughan L, Weisman HF, Sugiura S, Sagawa K, Levine JH. Effects of acute volume load on refractoriness and arrhythmia development in isolated chronically infarcted canine hearts. *Circulation* 1989;79:687–97.

24 Benditt DG, Kriett JM, Tobler HG, Gornick CC, Detloff BLS, Anderson RW. Electrophysiological effects of transient aortic occlusion in intact canine heart. *Am J Physiol* 1985;249:H1017–23.

25 Lab MJ. Contribution of mechano-electric coupling to ventricular arrhythmias during reduced perfusion. *Int J Microcirc Clin Exp* 1989;8:433–42.

26 Dean JW, Dilly SG, Lab MJ. Increased afterload shortens the absolute refractory period in situ left ventricle of anaesthetised pig. *J Physiol (Lond)* 1987;387:7P.

27 Reiter MJ, Synhorst DP, Mann DE. Electrophysiological effects of acute ventricular dilatation in the isolated rabbit heart. *Circ Res* 1988;62:554–62.

28 Hansen DE, Craig CS, Hondeghem LM. Stretch-induced arrhythmias in isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback. *Circulation* 1990;81:1094–105.

29 Calkins H, Maughan WL, Kass DA, Sagawa K, Levine JH. Electrophysiological effect of volume load in isolated canine hearts. *Am J Physiol* 1989;256:H1697–706.

30 Taggart P, Sutton PMI, Treasure T, *et al.* Contraction/excitation feedback in man? [abstract]. *Br Heart J* 1988; 59:109.

31 Taggart P, Sutton PMI, Treasure T, *et al.* Monophasic action potentials at discontinuation of cardiopulmonary bypass: evidence for contraction-excitation feedback in man. *Circulation* 1988;77:1266–75.

32 Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Changes in myocardial repolarization in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction-excitation feedback in humans. *Circulation* 1988;77:70–7.

33 Booth RW, Ryan JM, Mellet HC, Swiss E, Neth E. Hemodynamic changes associated with the Valsalva maneuver in normal men and women. *J Lab Clin Med* 1962;59:275–85.

34 Korner PI, Tonkin AM, Uther JB. Reflex and mechanical circulatory effects of graded Valsalva maneuvers in normal man. *J Appl Physiol* 1976;40:434–40.

35 Smith SA, Salih MM, Littler WA. Assessment of beat to beat changes in cardiac output during the Valsalva manoeuvre using electrical bioimpedance cardiography. *Clin Sci* 1987;72:423–8.

36 Hoffman BF, Cranefield PF, Lepeschkin E, Surawicz B, Herrlich HC. Comparison of cardiac monophasic potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;196:1297–301.

37 Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG. In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. *Eur Heart J* 1986;7:34–41.

38 Herman MV, Heinle RA, Klein MD, *et al.* Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. *N Engl J Med* 1967;222–32.

39 Herman MV, Gorlin R. Implications of left ventricular asynergy. *Am J Cardiol* 1969;23:538–47.

40 Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. *Circulation* 1974;50:121–7.

41 Autenrieth G, Surawicz B, Kuo CS. Sequence of repolarization of the ventricular surface in the dog. *Am Heart J* 1975;89:463–9.

42 Endresen K, Amlie JP, Forfang K, Simonsen S, Jensen O. Monophasic action potentials in patients with coronary artery disease: reproducibility of electrical restitution and of conduction at different stimulation rates. *Cardiovasc Res* 1987;21:696–702.

43 Reuter H. Localization of beta adrenergic receptors, and effects of noradrenaline and cyclic nucleotides on action potentials, ionic currents and tension in mammalian cardiac muscle. *J Physiol (Lond)* 1974;242:429–51.

44 Autenrieth G, Surawicz B, Kuo CS, Arita M. Primary T wave abnormalities caused by uniform and regional shortening of ventricular monophasic action potential in dog. *Circulation* 1975;51:668–76.

45 Taggart P, Sutton P, Lab M, Dean J, Harrison F. Interplay between adrenaline and interbeat interval on ventricular repolarisation in intact heart in vivo. *Cardiovasc Res* 1990;24:884–95.

46 Butrous GS, Butrous MS, Camm AJ. Dynamic interactions between heart rate and autonomic neural activities on the QT interval. In: Butrous GS, Schwartz PJ eds. *Clinical aspects of ventricular repolarization.* London: Farrand Press, 1989:139–50.

47 Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989;69:1049–169.

48 El-Sherif N, Gough W. Bradycardia-dependent early after depolarization and triggered activity. A mechanism for the arrhythmogenic effect of some drugs. In: Butrous GS, Schwartz PJ, eds. *Clinical aspects of ventricular repolarization.* London: Farrand Press, 1989:279–88.

49 Lab MJ, Dick DJ. Interval dependence of mechanically induced early afterdepolarisations in ventricle of anaesthetised pigs. *J Physiol (Lond)* (in press).

50 Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia: II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. *Circ Res* 1976; 39:168–77.

51 Gough WB, Mehra R, Restivo M, Zeiler RH, El-Sherif N. Reentrant ventricular arrhythmias in the late myocardial infarction period in the dog: correlation of activation and refractory maps. *Circ Res* 1985;57:432–42.

52 Olsson SB. Class III antiarrhythmic action. In: Vaughan Williams EM, ed. *Handbook of experimental pharmacology.* Berlin Springer Verlag, 1989:323–34.

53 Taggart P, Sutton PM, John RM, Horner S, Lab MJ, Swanton RH. Influence of ventricular loading and cycle length on ventricular repolarization in humans. *Circulation* 1990;82 (suppl III):55.

54 Schaper J, Schaper W. Ultrastructural correlates of reduced cardiac function in human heart disease. *Eur Heart J* 1983;4 (suppl A):35–42.

55 Francis GS. Neurohumoral mechanisms involved in congestive heart failure. *Am J Cardiol* 1985;55:15A–21A.

56 Stewart DE, Ikram H, Espiner EA, Nicholls MG. Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease. *Br Heart J* 1985;54:290–7.

57 Doherty JD, Cobbe SM. Electrophysiological changes in animal model of chronic cardiac failure. *Cardiovasc Res* 1990;24:309–16.

58 Dean JW, Lab MJ. Arrhythmia in heart failure: the role of mechanically induced changes in electrophysiology. *Lancet* 1989;i:1309–12.

59 Dean JW, Lab MJ. Effect of changes in load on monophasic action potential and segment length of pig heart in situ. *Cardiovasc Res* 1989;23:887–96.

Br Heart J 1992;67:230–5

β Endorphin release in patients after spontaneous and provoked acute myocardial ischaemia

Keith G Oldroyd, Kath Harvey, Christina E Gray, Graham H Beastall, Stuart M Cobbe

Abstract

***Background*—In animal models of circulatory shock and heart failure concentrations of the endogenous opioid peptide β endorphin are raised and opioid receptor blockade improves haemodynamic variables and survival. This study was performed to identify whether acute myocardial ischaemia provokes the release of β endorphin in humans.**

***Methods*—Observational study in a university cardiology centre. Serial measurements of β endorphin made by specific radioimmunoassay were correlated with other clinical and neuroendocrine variables that were measured prospectively. Fifty five patients with acute myocardial ischaemia and 26 patients undergoing elective coronary angioplasty of the left anterior descending coronary artery were studied.**

***Results*—β endorphin concentrations were raised above the upper limit of normal in 31/42 (74%) patients with confirmed myocardial infarction, 3/13 (23%) patients with unstable angina, and 10/24 (42%) patients after coronary angioplasty. There was no evidence of myocardial release of β endorphin. There were significant positive correlations between β endorphin and the concentrations of adrenocorticotrophic hormone, cortisol, and arginine vasopressin. In patients with acute myocardial ischaemia there was a significant positive correlation between the peak concentrations of creatine kinase and β endorphin but no correlation with visual analogue scores of the intensity of chest pain. The highest β endorphin concentrations were seen in patients whose clinical course was complicated by the development of heart failure.**

***Conclusions*—β endorphin release is a component of the neuroendocrine activation associated with myocardial ischaemia/infarction.**

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Guillemin *et al* showed in 1977 that rats release β endorphin concomitantly with adrenocorticotrophic hormone (ACTH) from the pituitary into the circulation in response to a range of stressful stimuli.[1] Shortly after this, co-release was confirmed in humans.[2 3] It has been known for over half a century that the cardiovascular system is extremely sensitive to exogenous opioids[4] and thus it was postulated that β endorphin release might be a pathogenetic factor in the haemodynamic derangements present in shock states. Animal models of circulatory shock have since been used to confirm β endorphin release after canine haemorrhagic[5 6] and endotoxic shock[7 8] and after both in primates.[9] Plasma β endorphin concentrations were much higher in dogs with experimental chronic heart failure than in control animals.[10] In humans, plasma β endorphin concentrations rise in response to insulin-induced hypoglycaemia,[11] intense physical exercise,[12] and surgery,[13] and they are raised in some patients with heart failure.[14] There are no published data on the response to myocardial ischaemia or infarction.

Patients

METHODS

To allow some clarification of the relation between the duration and severity of myocardial ischaemia and the release of β endorphin we studied two groups of patients.

Study 1

Fifty five consecutive patients admitted to the coronary care unit of Glasgow Royal Infirmary with a clinical diagnosis of acute myocardial ischaemia were studied. Myocardial infarction was confirmed by the presence of at least two of the three standard criteria: a compatible history of chest pain, typical evolving electrocardiographic changes, and an increase in the concentration of creatine kinase to above twice the upper limit of normal. Patients without these features but with evidence of ischaemia were considered to have unstable angina. Daily clinical examinations were performed and when there was evidence of pulmonary congestion radiological confirmation was sought. Cross sectional echocardiography was performed on day three, and where image quality allowed, we calculated the ejection fraction using apical two and four chamber views and a modified Simpson's formula.[15] Serial blood samples were taken from the time of admission to six weeks after discharge. Patients were asked to quantify the intensity of their chest pain on a 100 mm non-calibrated linear visual analogue scale cued with "very mild" and "very severe".

Study 2

Twenty six consecutive patients undergoing percutaneous transluminal angioplasty of the left anterior descending coronary artery were studied. Simultaneous aortic and coronary venous blood samples were taken for β endorphin and lactate estimation immediately before the first balloon dilatation (T_0) and at 2 (T_2) and 10 (T_{10}) minutes after the end of the procedure. Electrocardiographic leads I, II, III, aVR, aVL, and aVF were recorded continuously during each dilatation.

Assays

β Endorphin was measured by "in-house" radioimmunoassay after extraction from plasma by C_{18} Sep-Pak cartridges. The assay uses an ^{125}I-tracer and double antibody separation. The primary antiserum showed only 2% cross reactivity with human β lipotrophin (Peninsula Laboratories) during formal testing and <0·01% with α endorphin, γ endorphin, [leu]enkephalin, [met]enkephalin, ACTH, and dynorphin. The within batch coefficient of variation is 13·7% at a mean concentration of 3·2 pmol/l, improving to 2·3% at 42·5 pmol/l. Between batch precision is 5·8%, 5·3% and 4·9% at concentrations of 5·7, 10·2, and 43·7 pmol/l respectively. The normal range (mean (2SD)) of this assay in 60 volunteers sampled at 0900 hours is 2·5–7·2 pmol/l. The standard deviation of repeated measurements calculated by the method of Bland and Altman[16] is 0·5 pmol/l.

ACTH was measured by radioimmunoassay in unextracted plasma according to the method of Nicholson *et al*[17]: normal range at 0700–0900 hours <17 pmol/l. Cortisol was measured in a direct, solid-phase radioimmunoassay system[18]: normal range at 0700–0900 hours 280–720 nmol/l. Arginine vasopressin was extracted from plasma by C_{18} Sep-Pak cartridges and measured by radioimmunoassay.[19] Lactate was measured by a commercially available enzymatic assay (Boehringer Diagnostica). All samples for peptide assay were taken into chilled lithium heparin tubes with trasylol (1000 units/ml) added as a peptidase inhibitor for the β endorphin samples. After immediate separation in a refrigerated centrifuge 2 ml volumes of plasma for β endorphin assay were acidified with 0·5 ml 2M hydrochloric acid and flash frozen in either a dry ice/methanol bath or liquid nitrogen. All samples from individual patients were assayed in the same batch.

STATISTICAL ANALYSIS

The distribution of the data derived from this study were assessed by calculating the standardised coefficients of skewness and kurtosis. All of the variables were significantly skewed and so group values were expressed as medians with inter-quartile ranges. Groups were compared by Wilcoxon signed rank and Mann-Whitney U tests as appropriate. Univariate linear regression analysis between variables was performed by calculating Spearman rank correlation coefficients. For calculations we used a version of Statgraphics (STSC Inc) on a personal computer.

Results

STUDY 1

Fifty five consecutive patients (37 male, aged 37–75) admitted to the coronary care unit with acute myocardial ischaemia were studied. Raised plasma concentrations of β endorphin were detected in 31/42 (74%) patients with confirmed myocardial infarction (peak 12·0 (6·9–26·0) pmol/l) and in 3/13 (23%) patients with unstable angina (peak 4·5 (2·7–7·0) pmol/l) (fig 1). The highest concentration recorded was 98·8 pmol/l and occurred in a patient who subsequently developed cardiogenic shock and died. Figure 2 shows the time course of the change in β endorphin concentration for all 55 patients. There were no significant differences in β endorphin concentrations at any time point between patients who had and had not received thrombolytic therapy. The 12 patients with myocardial infarction who developed cardiac failure in hospital had a higher peak β endorphin concentration that those with an uncomplicated course (29·2 (9·9–51·5) *v* 9·6 (3·8–22·4) pmol/l (fig 1).

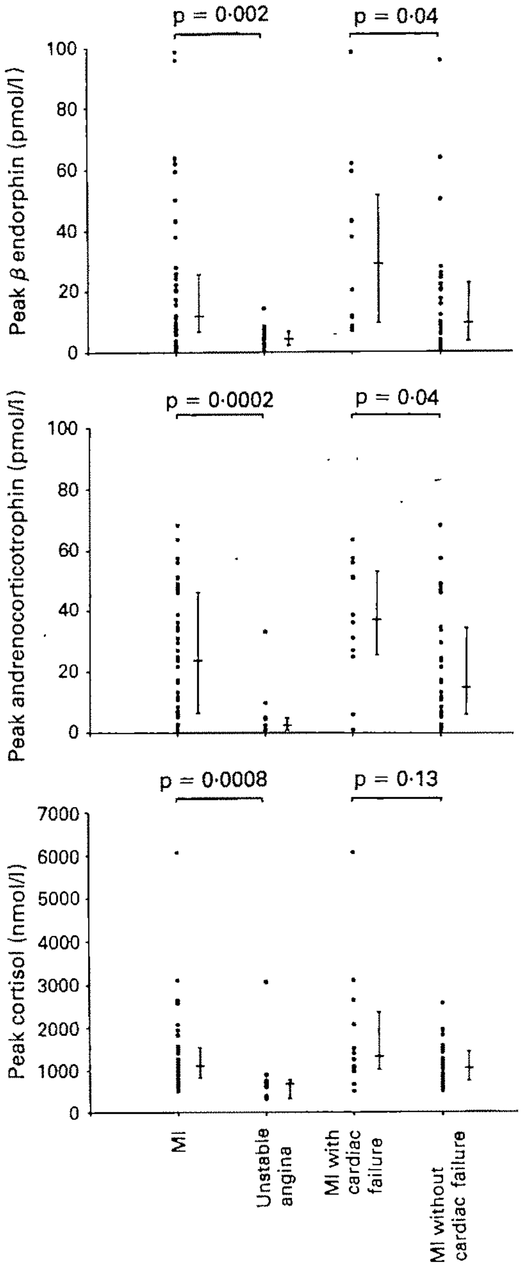

Figure 1 Peak concentrations of β endorphin, adrenocorticotrophic hormone, and cortisol in 55 patients with acute spontaneous myocardial ischaemia. Individual values are given with respective medians and interquartile range bars. MI, myocardial infarction.

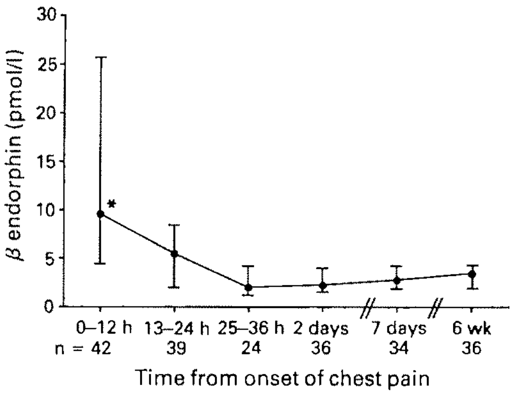

*Figure 2 Serial median (interquartile range) β endorphin concentrations in 55 patients with acute spontaneous myocardial ischaemia. *p < 0·001 v all other time points.*

Correlation between β endorphin and other neuroendocrine and clinical variables

Simultaneous measurements of other components of the hypothalamo-pituitary-adrenal axis provided a similar pattern of results to β endorphin. Thus peak ACTH and cortisol concentrations were 24·2 (6·6–47·0) *v* 2·5 (1·0–4·8) pmol/l and 1088 (824–1516) *v* 654 (323–742) nmol/l respectively for patients with myocardial infarction and without (fig 1). The highest concentrations of both β endorphin and ACTH were usually seen on admission and both returned to normal within 24 hours of admission in most patients (fig 2). Overall there was a good correlation between peak β endorphin and ACTH (r = 0·58, p = 0·00001), cortisol (r = 0·68, p = 0·00001) and glucose (r = 0·50, p = 0·001). Roughly equimolar concentrations of β endorphin and ACTH were seen, usually simultaneously, in 38/55 (69%) subjects. In 15 of these both were within the normal ranges (five with myocardial infarction) and in 23 one or both were raised. Several patients, however, showed a considerable difference between the concentrations of these two related hormones. In 12 (22%) peak ACTH was higher than normal and was 2–18 fold higher than the peak β endorphin concentration. In five the opposite pattern was seen, with peak β endorphin being 2–8 fold higher than peak ACTH. Figure 3 shows individual examples of these patterns.

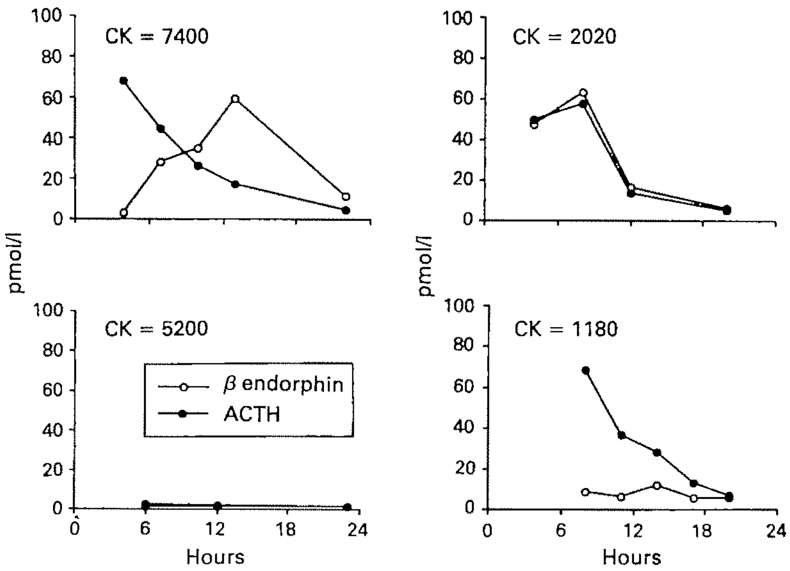

Figure 3 Individual patterns of β endorphin and adrenocorticotrophic hormone (ACTH) release in four patients with acute myocardial infarction. CK, creatine kinase (Iu/l).

The peak concentration of arginine vasopressin in patients with myocardial infarction was significantly higher than in patients with unstable angina (9·0 (3·3–17·8) *v* 1·0 (0·8–2·9) pg/ml (p = 0·0002)) and considering all patients peak arginine vasopressin correlated well with peak β endorphin (r = 0·59, p = 0·001).

Peak concentrations of β endorphin and creatine kinase were positively correlated (fig 4) and there was a negative correlation between the time from onset of symptoms to peak β endorphin concentrations (r = −0·38, p = 0·005). Though pain is a stimulus to β endorphin release, there was no significant correlation with pain scores. These were virtually identical in the patients with and without myocardial infarction (78 (65–86) *v* 76 (63–86) and those with and without cardiac failure (79 (57–84) *v* 78 (67–86)).

No significant correlations were seen with age, Norris score, ejection fraction on day three, and systolic or diastolic blood presure or heart rate on admission.

STUDY 2

All 26 patients had a technically successful angioplasty. In three patients concentrations of β endorphin in the great cardiac vein were > 1·0 pmol/l (2SD of the measurement error) higher than those in the aorta. But overall concentrations in the aorta and great cardiac vein were similar at both time points. There was thus no consistent evidence of any myocardial release and accordingly only the concentrations in the great cardiac vein are reported. At T_0 only two patients had β endorphin concentrations > 7·2 pmol/l (upper limit of normal): one of these had an episode of severe angina during transfer to the catheter laboratory and the other had a difficult arterial cannulation. Both of these patients were excluded from further analysis.

Before angioplasty the β endorphin concentration was 3·2 (2·4–4·9) pmol/l rising to 4·5 (3·4–13·8) pmol/l at T_{10}, p = 0·002. The concentrations changed by > 1·0 pmol/l in 16 patients: in 14 (58%) concentrations rose and in two (8%) they fell. At T_{10} 10/24 (42%) patients had concentrations > 7·2 pmol/l. The percentage change for all 24 patients was 62 (14–193)%. In the 14 patients showing increases in β endorphin the percentage change was 158 (73–248)%. The peak concentration of β endorphin after angioplasty was 4·6 (3·4–16·0) pmol/l, significantly lower than after myocardial infarction (p = 0·02).

Correlation between β endorphin and other neuroendocrine and clinical variables

As in the patients with spontaneous myocardial ischaemia, significant positive correlations were found between concentrations of β endorphin in the great cardiac vein and concentrations of ACTH ($r = 0\cdot85$, $p = 0\cdot0001$) and cortisol ($r = 0\cdot72$, $p = 0\cdot001$). No correlation was apparent between simultaneous measurements of β endorphin and lactate concentrations in the great cardiac vein ($r = 0\cdot06$, $p = 0\cdot76$) but there was a weak positive correlation with lactate extraction ($r = 0\cdot43$, $p = 0\cdot047$). There was a significant negative correlation between β endorphin concentration and the total duration of balloon occlusions ($r = -0\cdot69$, $p = 0\cdot0009$) but no correlation with the maximum ST segment deviation recorded during angioplasty ($r = 0\cdot002$, $p = 0\cdot99$).

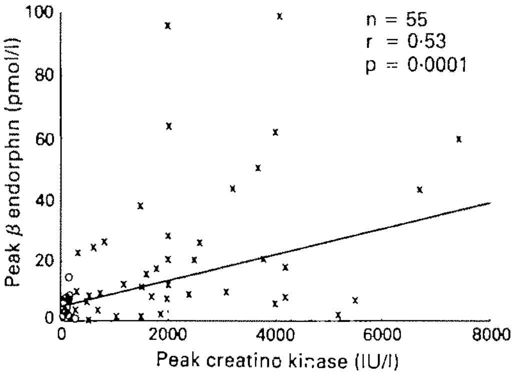

Figure 4 Correlation between peak concentration of β endorphin and creatine kinase in 55 patients with acute myocardial ischaemia. x, *myocardial infarction;* O, *no myocardial infarction.*

Discussion

β Endorphin and ACTH have a common origin for pituitary pro-opiomelanocortin. They are stored together in the secretory granules of the pituitary corticotrophs and are co-released in response to stressful stimuli.[20] The unexpected dichotomy seen in some of our patients has, however, been described in other disease states.[21,22] This absence of molar unity may be related to the different plasma half-lives of β endorphin, β lipotrophin, and ACTH[23,24] and also to inter-individual variation in the post-translational processing of the precursor[25,26] which follows the application of a stressful stimulus.

Which component(s) of the stimulus of myocardial ischaemia provoke(s) β endorphin release and which if any are important in determining the pattern of the neuroendocrine response? In the patients with acute myocardial infarction and therefore prolonged periods of coronary artery occlusion there was a weak correlation between β endorphin concentrations and creatine kinase, a marker of ischaemic damage. There was a negative correlation between the duration of ischaemia (assessed from patient symptoms) and β endorphin concentrations. This latter finding suggests that β endorphin is released as a single pulse at the onset of myocardial ischaemia with the highest concentrations being found the earlier the patient is seen. In the angioplasty patients, in whom the period of coronary artery occlusion was much shorter, there was again only a weak correlation between β endorphin and a biochemical marker of ischaemia and no correlation at all with the electrical evidence of ischaemia. The persistence of a negative correlation with the duration of ischaemia (balloon inflation time) in this second patient group is consistent with the release of a single pulse of β endorphin—in this case within minutes of the ischaemic stress being applied. In the patients with unstable angina, myocardial ischaemia was present but there was virtually no β endorphin release. Thus overall there is no convincing evidence that the β endorphin release is primarily determined by either the duration or the objective severity of the ischaemic insult.

What of the patient's perception of the ischaemic insult? Despite widely differing β endorphin concentrations, pain scores in the patients with myocardial infarction and unstable angina were virtually identical and overall there was no correlation between these scores and β endorphin concentrations. Visual analogue scales are a relatively crude method of assessing pain perception and it is possible that more complex techniques might have revealed a closer relation between perceived pain and β endorphin release. However, alternative stimuli such as nausea, transient blood pressure fluctuations, or the degree of activation of the autonomic nervous system might be involved.

There is good evidence that β endorphin release has a pathophysiological role in certain disease states and is not just an epiphenomenon. In various animal models of circulatory collapse including anaphylaxis,[27] hypovolaemia (haemorrhage),[28,29] and septicaemia,[30,31] naloxone and a range of other opioid receptor antagonists produce improved haemodynamic performance and substantial improvements in survival. A predominantly central mode of action is suggested by the lesser effects of analogues unable to cross the blood-brain barrier. Peripheral effects, however, may be important. Thus direct intracoronary infusion of naloxone in normal dogs results in dose-dependent increases in developed tension, left ventricular dP/dt, cardiac output, and blood pressure that are not reproducible with the inactive (+)-isomer.[32,33] The critical dependence of the response to naloxone on the presence of pituitary derived endorphins has been confirmed by Holaday *et al* who gave intracerebroventricular injections of naloxone to rats subjected to hypovolaemia. The dramatic recovery of blood pressure seen was completely abolished by prior hypophysectomy.[34]

There are relatively few studies of the effects of opioid receptor blockade in primary cardiac disease. In a canine model of chronic cardiac failure plasma concentrations of β endorphin were much higher than in control animals and the intravenous administration of nalmafene, a potent opioid receptor antagonist,[35] resulted in a further rise in β endorphin as well as increases in ACTH; catecholamines; mean arterial pressure; cardiac output; left ventricular dP/dt; and regional blood flow to the myocardium, skeletal muscle (quadriceps), and kidney. Sympathetic blockade abolished these effects, suggesting that the beneficial effects of opioid antagonists in this model are mediated via the sympathetic nervous system.[10] In subsequent studies this group showed that the action of naloxone was preserved in anaesthetised animals, indicating that the effects were not related to removal of the antinociceptive action of the endogenous opioids.[36] Physiological concentrations of β endorphin selectively stimulate aldosterone secretion in dogs and could have a role in the modulation of sodium balance after myocardial infarction and in heart failure.[37] Also in a canine model it has been shown that the systemic and coronary vasoconstriction which follows the intracerebral administration of the opiate agonist fentanyl is mediated via the release of arginine vasopressin.[38] Our data showing a correlation between β endorphin and arginine vasopressin concentrations are consistent with this finding.

There are several anecdotal reports of improvements in blood pressure in patients with septicaemic[39] and cardiogenic shock[40,41] after the administration of intravenous naloxone. A recent double blind controlled study showed some benefit of naloxone in septicaemic shock.[42] Naloxone and some other opioid receptor ligands have another property that might be of relevance in cardiovascular disease. They showed antiarrhythmic activity in rats subjected to coronary artery ligation.[43] Interestingly, β endorphin at concentrations in the pmol/l range provokes a range of arrhythmias, mainly atrial, in isolated perfused rat hearts.[44] The arrhythmogenic action of β endorphin in this model is naloxone-reversible, but in most animals the concentrations of naloxone required to show cardiac electrophysiological and/or antiarrhythmic effects greatly exceeds the concentrations at which complete opioid receptor blockade would be expected. Thus it is likely that these effects are non-specific and unrelated to opioid receptor antagonism.[45,46]

We have shown, for the first time, that β endorphin release is a component of the neuroendocrine activation associated with myocardial ischaemia/infarction. The demonstration of a pathophysiological role in these particular clinical syndromes must await the results of further studies.

KGO is a British Heart Foundation junior research fellow.

1 Guillemin R, Vargo TM, Rossier J, *et al.* β-endorphin and adrenocroticotrophin are secreted concomitantly by the pituitary gland. *Science* 1977;197:1367–9.

2 Nakao K, Nakai Y, Oki S, Horii K, Imura H. Presence of immunoreactive β-endorphin in normal human plasma. A concomitant release with adrenocorticotrophin after metyrapone administration. *J Clin Invest* 1978;62:1395–8.

3 Mullen PE, Jeffcoate WJ, Linsell C, Howard R, Lees LH. The circadian variation of immunoreactive lipotrophin and its relationship to ACTH and growth hormone in man. *Clin Endocrinol* 1979;11:533–9.

4 Gruber CM, Robinson PI. Studies on the influence of morphine, papaverine and quinidine upon the heart. *J Pharmacol Exp Ther* 1929;37:429–49.

5 Bruckner UB, Lang RE, Ganten D. Release of opioid peptides in canine hemorrhagic hypotension: effects of naloxone. *Res Exp Med* 1984;184:171–8.

6 Vargish T, Beamer K. Hemodynamic effects of naloxone in early canine hypovolemic shock. *Circ Shock* 1985;17:45–57.

7 Bone RC, Jacobs ER, Potter DM, *et al.* Endorphins in endotoxin shock. *Microcirculation* 1981;1:285–9.

8 Evans SF, Medbak S, Hinds CJ, *et al.* Plasma levels and biochemical characterisation of circulatory [met]-enkephalin in canine endotoxin shock. *Life Sci* 1984;34:1481–6.

9 Gurll NJ, Reynolds DG, Holaday JW. Evidence for a role of endorphins in the cardiovascular pathophysiology of primate shock. *Crit Care Med* 1988;16:521–30.

10 Liang C-s, Imai N, Stone CK, Woolf PD, Kawashima S, Tuttle R. The role of endogenous opioids in congestive heart failure; effects of nalmafene on systemic and regional hemodynamics in dogs. *Circulation* 1987;75:443–51.

11 Nakao K, Nakai Y, Jingami H, *et al.* Substantial rise of plasma β-endorphin levels after insultin-induced hypoglycaemia in human subjects. *J Clin Endocrinol Metab* 1979;49:838–41.

12 Carr DB, Bullen BA, Skrinar GS, *et al.* Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. *N Engl J Med* 1981;305:560–3.

13 Smith R, Besser GH, Rees LH. The effect of surgery on plasma β-endorphin and methionine-enkephalin. *Neurosci Lett* 1985;55:289–92.

14 Kawashima S, Fukutake N, Nishian K, Asakuma S, Iwasaki T. Elevated plasma β-endorphin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1991;17:53–8.

15 Starling MR, Crawford MH, Sorenson SG, Levi B, Richards KL, O'Rourke RA. Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. *Circulation* 1981;63:1075–83.

16 Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.

17 Nicholson WE, Davis DR, Sherrell BJ, Orth DN. Rapid radioimmunoassay for corticotrophin in unextracted human plasma. *Clin Chem* 1984;30:259–65.

18 McConway MG, Chapman R. Development and evaluation of a simple, direct, solid-phase radioimmunoassay of serum cortisol from readily available reagents. *Clin Chim Acta* 1986;158:59–70.

19 Morton JJ, Connell JMC, Hughes MJ, Inglis GC, Wallace ECH. The role of plasma osmolality, angiotension II and dopamine in vasopressin release in man. *Clin Endocrinol (Oxf)* 1985;23:129–38.

20 Owens PC, Smith R. Opioid peptides in blood and cerebrospinal fluid during acute stress. Baillière's *Clinical Endocrinology and Metabolism*. 1987;1:415–37.

21 Jeffcoate WJ, Rees LH, McLoughlin L, *et al.* β-endorphin in human cerebrospinal fluid. *Lancet* 1978;ii:119–21.

22 Hinds CJ, Evans SF, Varley JG, Tomlin S, Rees LH. Neuroendocrine and cardiovascular changes in septic shock: effect of high-dose corticosteroid therapy. *Circ Shock* 1985;15:61–72.

23 Aronin N, Wiesen M, Liotta AS, Schussler GC, Krieger TD. Comparative clearance rates of β-endorphin and β-lipotropin in humans. *Life Sci* 1981;29:1265–9.

24 Liotta AS, Li CH, Schussler GC, Krieger DT. Comparative clearance rate, volume of distribution and plasma half-life of human β-lipotropin and ACTH. *Life Sci* 1978;23:2323–30.

25 Imura H, Kato Y, Nakai Y, *et al.* Endogenous opioids and related peptides: from molecular biology to clinical medicine. *J Endocrinol* 1985;107:147–57.

26 Shiomi H, Watson SJ, Kelsey JE, Akil H. Pretranslational and posttranslational mechanisms for regulating β-endorphin-adrenocorticotrophin of the anterior pituitary lobe. *Endocrinology* 1986;119:1793–9.

27 Amir S. Opiate antagonists improve survival in anaphylactic shock. *Eur J Pharmacol* 1982;80:161–2.

28 Faden AI, Holaday JW. Opiate antagonists: a role in the treatment of hypovolemic shock. *Science* 1979;205:317–8.

29 Vargish T, Reynolds DG, Gurll NJ, *et al.* Naloxone reversal of hypovolemic shock in dogs. *Circ Shock* 1989;7:31–8.

30 Holaday JW, Faden AI. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. *Nature* 1978;275:450–1.

31 Faden AI, Holaday JW. Naloxone treatment of endotoxin shock: Stereospecificity of physiologic and pharmacologic effects in the rat. *J Pharmacol Exp Ther* 1980;212:441–7.

32 Caffrey JL, Gaugl JF, Jones CE. Local endogenous opiate activity in dog myocardium: receptor blockade with naloxone. *Am J Physiol* 1985;248:H382–8.

33 Lechner RB, Gurll NJ, Reynolds DG. Intracoronary naloxone in hemorrhagic shock: dose-dependent stereospecific effects. *Am J Physiol* 1985;249:H272–7.

34 Holaday JW, O'Hara M, Faden AI. Hypophysectomy alters cardiorespiratory variables: central effects of pituitary endorphins in shock. *Am J Physiol* 1981;241:H479–85.

35 Dixon R, Howes J, Gentile J, *et al.* Nalmafene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986;39:49–53.

36 Sukamoto S, Stone CK, Woolf PD, Liang C-S. Opiate receptor antagonism in right-sided congestive heart failure. *Circ Res* 1989;65:103–14.

37 Güllner H-G, Gill JR Jr. Beta-endorphin selectively stimulates aldosterone secretion in hypophysectomised, nephrectomised dogs. *J Clin Invest* 1983;71:124–8.

38 Pasyk S, Grekin RJ, Walton JA, Pluta W, Pitt B. Mechanism of opiate mediated systemic and coronary vasoconstriction [abstract]. *Am J Cardiol* 1982;49:940.

39 Peters WP, Johnson MW, Friedman PA, Mitch WE. Pressor effect of naloxone in septic shock. *Lancet* 1981;i:529–32.

40 Dirksen R, Otten MH, Wood GJ, *et al.* Naloxone in shock. *Lancet* 1980;ii:1360–1.

41 Higgins TL, Sivak ED. Reversal of hypotension with

naloxone. *Cleve Clin Q* 1981;**48**:283–8.
42 Roberts DE, Dobson KE, Hall KW, Bruce Light R. Effects of prolonged naloxone infusion in septic shock. *Lancet* 1988;**ii**:699–702.
43 Sitsapesan R, Parratt JR. The effects of drugs interacting with opioid receptors on the early ventricular arrhythmias arising from myocardial ischaemia. *Br J Pharmacol* 1989;**97**:795–800.
44 Lee AYS, Zhan CY, Wong TM. Effects of β-endorphin on the contraction and electrical activity of the isolated perfused rat heart. *Int J Pept Protein Res* 1984;24:525–8.
45 Brasch H. Influence of the optical isomers (+)- and (−)-naloxone on beating frequency, contractile force and action potentials of guinea-pig isolated cardiac preparations. *Br J Pharmacol* 1986;**88**:733–40.
46 Oldroyd KG, Hicks MH, Cobbe SM. The class III antiarrhythmic effects of opioid receptor ligands are not receptor mediated [abstract]. *Eur Heart J* 1990;11:400.

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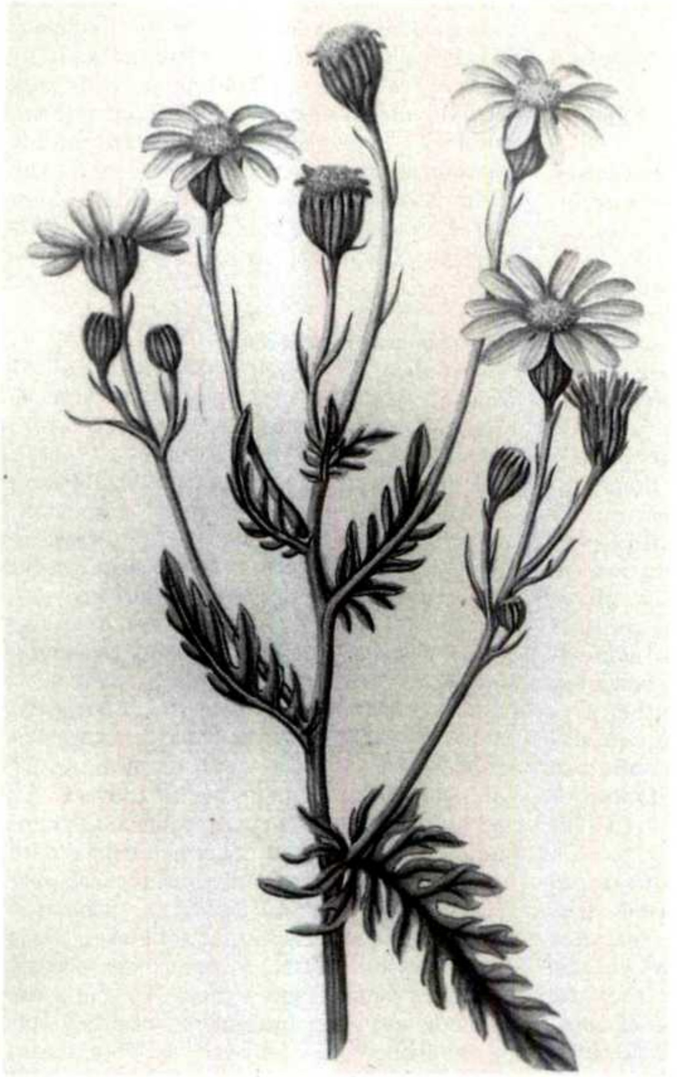
PLANTS IN CARDIOLOGY



Senecio jacobaea L. *Flora Danicae* Hafnia: Môllerus, 1787: volume 6; plate 944.

Dietary pulmonary hypertension

The idea that certain plants could produce pulmonary hypertension seemed so unlikely that I began to wonder just how this discovery had been made. The story began in Iowa in 1884 when a new disease of horses with hepatic cirrhosis was traced to the ingestion of *Crotalaria sagittalis* (Leguminosae) the native species of the rattlebox plant which was grown as green manure to improve the sandy soil. In1921 *C spectabilis* was introduced from India and it caused many outbreaks of disease among farm animals in the southern United States. Lesions in cows, pigs, goats, chickens, and horses included subendocardial haemorrhage, thickened pulmonary alveoli, pulmonary oedema, anaemia, and renal and hepatic disease. *Senecio* (Compositae) also caused equine cirrhosis in South Africa in 1920, while in North America the tar weed *Atalaya* (Sapindaceae), alsike clover *Trifolium* (Leguminosae), and *Amsinckia* (Boraginaceae) caused it too. A recent human epidemic of cirrhosis in India followed the accidental ingestion of *Heliotropium* (Boraginaceae). All these different genera and families contain pyrrolizidine alkaloids.

But none of these studies of natural or induced disease reported cardiac hypertrophy or pulmonary arterial disease. However, in 1955 Schoental and Head produced pulmonary infarction in rats with *Crotalaria*. Then in 1961 the breakthrough came when J J Lalich in Madison showed that rats fed *Crotalaria* seed or its alkaloid monocrotaline developed acute pulmonary arteritis. He went on to pioneer the crucial long term study. The rats developed intimal and muscular thickening of the pulmonary arterioles, dilated pulmonary arteries and right ventricular hypertrophy. In 1967 Kay, Harris, and Heath in Birmingham were the first to measure the right heart pressure in treated rats and confirm pulmonary hypertension. Later it was shown that the British plant, ragwort, *Senecio jacobaea*, sold in health stores for coughs and colds, produced pulmonary hypertension in rats. Meanwhile Bras and his colleagues had discovered that cirrhosis in Jamaican children was caused by hepatic veno-occlusive disease and they showed that the histology of their patients was identical with that of animals with *Crotalaria* and *Senecio* poisoning. Jamaican children often drank "bush-tea" made from these plants. But pulmonary hypertension has never been found in patients with veno-occlusive cirrhosis. Maybe only rats are susceptible. Donald Heath has recently looked back over his 25 years work on dietary pulmonary hypertension (*Circulation Research* 1991;**25**: 973–74).

Again, as with sweet clover disease of cattle (*British Heart Journal* 1991;**66**:181), a leguminous plant introduced from abroad for farming purposes has led via veterinary medicine to an important cardiovascular discovery.

A HOLLMAN

Br Heart J 1992;67:236–9

Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis

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Abstract

***Objective*—To identify valvar heart disease in patients with chronic uraemia by conventional and colour coded Doppler echocardiography.**

***Design*—Case series of an unselected group of 62 patients with end stage renal failure.**

***Setting*—Centre for haemodialysis in a referral hospital in Switzerland.**

***Patients*—62 patients on chronic haemodialysis.**

***Main outcome measures*—Frequency of structural and functional valve abnormalities and their relation to clinical findings.**

***Results*—Structural changes were seen in 40 (64%) of 62 patients after 50 months (range 3–178 months) on haemodialysis. The mitral annulus and aortic cusps were thickened in 25 (40%) and in 34 (55%) patients respectively. Aortic stenosis was present in eight (mean (SD) age 60·5 (8·5) years), with a maximal instantaneous pressure gradient of 41 (14) mm Hg. Aortic regurgitation was seen in eight, mitral regurgitation in seven, and mitral stenosis in three patients. Patients with aortic stenosis had been on haemodialysis for significantly longer than the remaining patients (101 (43) *v* 46 (43) months, $p = 0.01$) and had significantly higher concentrations of serum alkaline phosphatase (176 (89) *v* 117 (47) IU/l, $p < 0.01$) and of parathyroid hormone (54 (66) *v* 19 (29) ng/ml, $p < 0.02$).**

***Conclusions*—Patients on long-term haemodialysis had an increased frequency of haemodynamically relevant changes in the aortic and mitral valves. The degenerative valve disease may be related in part to the duration of haemodialysis and to alterations in calcium metabolism as indicated by increased plasma concentrations of alkaline phosphatase and parathyroid hormone.**

Valve disease is an under-recognised complication of chronic uraemia.[1] Calcification of the mitral annulus was more common in patients with chronic renal failure than in age-matched controls.[2–5] Calcification of the mitral annulus can cause mitral regurgitation[2] or stenosis or both[3 6] and is also often associated with aortic valve calcification.[6 7] Severe aortic valve calcification can cause aortic stenosis[8–10] and aortic regurgitation.[11] Calcification of the mitral and aortic valves can occur prematurely in patients with chronic uraemia on long-term haemodialysis.[2 3 5] The cause of premature calcification of the mitral and aortic valves are uncertain; however, secondary hyperparathyroidism, hypertension,[12] and hypercholesterolaemia[13] are thought to be essential risk factors. There are few data on the frequency of Doppler detected haemodynamically relevant valvar complications in end stage renal disease. We examined the frequency and aetiology of calcified, haemodynamically relevant aortic and mitral valve stenosis and regurgitation and its relation to clinical findings in an unselected population of patients on long-term haemodialysis.

Patients and methods

We studied 62 patients (31 men and 31 women) aged 55 (14) years who had been receiving maintenance haemodialysis (9–12 h/week) for 50 (47) months (range 3–178). The primary cause of end stage renal disease was analgesic nephropathy in 22, glomerular nephritis in 13, polycystic kidney disease in eight, pyelonephritis in five, diabetes mellitus in five, and other or unknown underlying renal disease in nine. Conventional and colour coded Doppler echocardiographic examinations were performed just after haemodialysis on a Toshiba 160 equipment with 2·5 and 3·5 MHz transducers. The two echocardiographers were unaware of the clinical details. M mode, cross sectional, and conventional and colour coded Doppler echocardiograms and measurements were obtained by standard techniques. All video and paper records were reviewed by three cardiologists. Structural alterations in the cusps and annuluses of the aortic and mitral valves were diagnosed by thickened and bright echoes on both the M mode and cross sectional echocardiograms by established diagnostic criteria.[14] Significant aortic stenosis was defined as cusp separation of less than 15 mm and a maximum aortic flow velocity greater than 2·2 m/s. Significant regurgitation was defined as a regurgitation jet on the colour and pulsed Doppler echocardiograms extending more than 2 cm behind the plane of the aortic, mitral, or tricuspid valve and pandiastolic (aortic regurgitation) or pansystolic (mitral and tricuspid regurgitation) regurgitant flow of more than 2 m/s on continuous wave Doppler. Regurgitation was classified as mild, moderate, or severe on the basis of the extent to which retrograde flow filled the atrium or ventricle (less than one third, one to two thirds, more than two

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thirds). The following blood tests were done before dialysis: haemoglobin, creatinine, total cholesterol, total calcium, phosphate, alkaline phosphatase (normal value < 174 U/l), parathyroid hormone (carboxyl terminal RIA, normal value 0·4–1·5 ng/ml). The mean predialysis calcium-phosphate product (mmol/l) was calculated from the monthly determinations during the 12 months before echocardiography.

The clinical data were collected by an experienced physician. Results were expressed as mean (SD). The data were analysed by an unpaired *t* test. A p value of < 0·05 was considered statistically significant.

Results

Table 1 shows the clinical features of patients with and without aortic and/or mitral valve abnormalities. Patients with structural abnormalities of aortic valve and/or mitral valve were older (59·5 (11·6) years, n = 40) than patients with normal valves (46 (13·5) n = 22). Aortic and mitral valve abnormalities were not associated with a higher incidence of hypertension. There was a history of hypertension in 30 (75%) of 40 patients with aortic and/or mitral valve abnormalities and in 49 (79%) of all patients (table 1).

The interval since diagnosis of hypertension was similar in patients with and without structural abnormalities of the valves (10·9 (6·4) *v* 8·7 (6·8) years) but there was a tendency for hypertension to have been present longer in patients with mitral valve abnormalities than in those without.

There was no association between the aetiology of end stage renal disease and aortic or mitral valve disease. No patient gave a history for previous rheumatic fever or infective endocarditis. Echocardiographically abnormal and thickened aortic and mitral valves (including the mitral annulus) with bright echoes were seen in 40 (64%) of the 62 patients (table 2). Twenty five patients (40%) had an altered mitral valve apparatus (at least thickened mitral annulus). In 34 patients (55%) one or more aortic cusps were thickened and all cusps were thickened in 17 (27%). Nineteen (76%) of the 25 patients with mitral valve abnormalities also had calcification of the aortic valve.

Seventeen (43%) of the 40 patients with structural valve abnormalities had a total of 26 abnormal Doppler echocardiographic findings associated with the aortic or mitral valve (table 3).

Table 2 Frequency of echocardiographically confirmed aortic and mitral valve abnormalities (valve calcification) in 62 patients with end stage renal disease

Echocardiographic finding	*Number of patients*	*Frequency of MVA/AVA (%)*
No valve alterations	22	—
All valve alterations (MVA, AVA)	40	65
MVA	25	40
AVA:		
1 cusp	34	55
3 cusps	17	27
MVA and AVA combined	19	31

AVA, aortic valve abnormality; MVA, mitral valve abnormality.

AORTIC STENOSIS

Aortic stenosis was present in three men and five women (8/62, (13%)). Maximal aortic flow ranged from 2·4 to 4·0 m/s resulting in a maximal instantaneous pressure gradient of 41 (14) mm Hg (range 23–64 mm Hg). Systolic blood pressure, systolic separation of the aortic valve, and fractional shortening were significantly lower and posterior wall thickness was higher in patients with aortic stenosis than in the remaining patients; there was no age difference, however (table 4).

Aortic stenosis was associated with longer duration on dialysis (p < 0·01), higher serum alkaline phosphatase concentrations (p < 0·01), and higher serum concentrations of parathyroid hormone (p < 0·02), but it was not associated with a higher calcium-phosphate product (table 4) or the underlying kidney disease.

AORTIC REGURGITATION

Aortic regurgitation was present in three patients with predominantly aortic stenosis and in one patient with mitral regurgitation, and in four other patients (all with structural abnormalities of the aortic valve). Regurgitation was mild in four of the eight patients and was moderate in four.

MITRAL REGURGITATION

Mitral regurgitation was present in seven patients. Six of them had mitral valve abnormalities, one had left ventricular dilatation with

Table 1 Comparison of patients with and without structural abnormalities of the aortic and mitral valves (mean (SD))

Variable	*All*	*No AVA/MVA*	*AVA*	*MVA*	*AVA/MVA*
n (%)	62	22 (35)	34 (55)	25 (40)	40 (65)
Age at study (yr)	55·2 (13·5)	46·9 (13·1)	59·0 (12·4)‡	62·9 (6·8)‡	59·5 (11·4)‡
Months on dialysis	50·4 (46·1)	35·7 (41·6)	56·8 (49·1)	71·2 (50·7)†	57·0 (48·1)
Hours on dialysis (per week)	10·0 (2·0)	9·7 (2·5)	10·3 (1·7)	10·2 (1·7)	10·2 (1·7)
History of hypertension (n)	49	19	26	17	30
Years of hypertension	10·0 (6·6)	8·7 (6·8)	10·3 (5·6)	13·3 (6·7)*	10·9 (6·4)
Systolic blood pressure (mm Hg)	142 (20)	144 (19)	141 (21)	140 (22)	141 (20)
Diastolic blood pressure (mm Hg)	83 (11)	83 (9)	83 (12)	82 (11)	83 (12)
Haemoglobin (g/l)	101 (1·7)	99 (1·8)	102 (1·6)	101 (1·6)	102 (1·6)
Creatinine (μmol/l)	914 (201)	975 (203)	904 (195)	821 (196)	879 (191)
Calcium × phosphate product (mmol/l)	4·4 (0·9)	4·6 (0·9)	4·3 (0·9)	4·4 (0·4)	4·3 (0·9)
Alkaline phosphatase (U/l)	129 (67)	131 (73)	134 (67)	133 (72)	129 (63)
Parathyroid hormone (ng/ml)	22 (37)	20 (34)	25 (41)	22 (40)	23 (38)

*p = 0·05 *v* no AVA/MVA; †p < 0·05 *v* no AVA/MVA; ‡p < 0·01 *v* no AVA/MVA.
AVA, aortic valve abnormality; MVA, mitral valve abnormality; AVA/MVA, any abnormality of aortic and/or mitral valves; no AVA/MVA, neither aortic nor mitral valve abnormality.

Table 3 Results based on Doppler echocardiograms in 17 patients with important valve dysfunction (n = 26)

		Type of valve dysfunction (n = 26)			
		AS (8)	*AR (8)*	*MR (7)*	*MS (3)*
Total number of patients	(n = 17)				
With isolated valve dysfunction	(n = 13):				
5		X			
4			X		
3				X	
1					X
With combined valve dysfunction	(n = 4):				
1		X		X	
1		X	X	X	
2		X	X	X	X

AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis.

Table 4 Findings in patients with and without aortic stenosis (mean (SD))

Variable	*AS (n = 8)*	*No AS (n = 54)*	*p*
Months on dialysis	101 (43)	46 (43)	0·01
Systolic blood pressure (mm Hg)	125 (19)	144 (19)	<0·01
Aortic cusp separation (mm)	10 (3)	20 (3)	<0·001
Posterior wall thickness (mm)	14·3 (1·7)	12·2 (2·1)	<0·01
Left ventricular fractional shortening (%)	30·0 (1·8)	35·9 (7·0)	<0·03
Parathyroid hormone (ng/ml)	54 (66)*	19 (29)	<0·02
Alkaline phosphatase (U/l)	176 (98)	117 (47)	<0·01
Calcium × phosphate product (mmol/l)	4·3 (0·6)	4·5 (1·0)	NS

*n = 7, one patient who had had a parathyroidectomy was not included.
AS, aortic stenosis.

global hypokinesia and on a dilated annulus. Regurgitation was moderate in five and severe in two. Three patients had isolated (moderate) mitral regurgitation.

MITRAL STENOSIS

One patient had mild isolated mitral stenosis (Doppler derived mitral valve area 1·9 cm^2) and two patients had moderate mitral stenosis (1·4 and 1·3 cm^2) associated with mitral regurgitation, aortic stenosis, and aortic regurgitation.

TRICUSPID REGURGITATION

Mild to moderate tricuspid valve regurgitation was seen in five patients and was associated with other valve diseases in four: one with aortic stenosis, one with aortic regurgitation, one with mitral regurgitation, and one with combined aortic and mitral valve disease.

A COMPARISON OF CLINICAL AND DOPPLER ECHOCARDIOGRAPHIC DIAGNOSIS OF VALVE DISEASE

The clinical diagnosis of aortic stenosis was correct in five, falsely negative in three, and falsely positive in five, when conventional and colour coded Doppler ultrasound were used as the reference standard. Aortic regurgitation and mitral stenosis were not diagnosed clinically in any patient; mitral regurgitation was correctly diagnosed in three, was falsely negative in three and falsely positive in four patients. The clinical diagnosis was correct if valve disease was severe (both patients with aortic stenosis and pressure gradients greater than 60 mm Hg and both patients with mitral regurgitation grade III).

Discussion

In keeping with several earlier studies[15–18] our data show a high frequency (40/62) of structural alterations of the aortic and mitral valve apparatus caused by degeneration and calcification of valve structures in patients with progressive renal failure. Furthermore 43% of our patients with structural valve changes also had Doppler echocardiographic evidence of functional abnormalities. Four patients had combined aortic and mitral valve diseases. Most importantly, aortic stenosis was present in eight of the 62 patients. This is more than expected from the estimated frequency of valve disease in the general population.[19 20] Despite the more stringent diagnostic criteria for aortic stenosis in our study the frequency in patients with chronic renal failure and long term haemodialysis was higher than reported by others.[1] The mean age and duration of haemodialysis resembled the findings in a comparable study by Maher *et al.*[21] One fourth of our patients with calcified aortic valves—the same proportion as reported by Bryg *et al*[11]—had mild aortic regurgitation of no or little clinical relevance. Our finding that 40% had abnormal mitral valves accords with other reports[7 12]; however, the frequency of regurgitation (24% of mitral valve abnormalities) differs from the report by Bryg, who found that 37% of patients with calcification of the mitral annulus had mitral regurgitation.[11] Labovitz *et al* reported that 55% of patients with a calcified mitral annulus had mitral regurgitation.[22] This discrepancy may be partly explained by the fact that in our study Doppler echocardiography was performed after haemodialysis—that is, without or at a reduced volume overload. Degeneration and calcification of tricuspid aortic valves without rheumatic changes is an unusual cause of aortic stenosis in patients under the age of 70.[23 24] The mean (SD) age of our study population was 55·2 (13·5) years. Though our patients with abnormal aortic or mitral valves were older than patients without (table 1), those with functional abnormalities were almost the same age as those with only structural changes (61·4 (6·8), n = 17 *v* 59·5 (11·4) n = 23). However, we found a strong correlation between the duration of haemodialysis treatment and the development of aortic stenosis. Patients with aortic stenosis had been more than twice as long on haemodialysis as those without ($p < 0·001$). Duration of haemodialysis was also an independent predictor of structural abnormalities of the aortic and mitral valves in another study and was associated with premature valve calcification.[21] The duration of renal failure and subsequent haemodialysis may cause mechanical stress on valves mainly through hypertension and increased cardiac output (anaemia, arteriovenous fistula) causing further valve changes. In addition, slight inequalities in cusp size, which Roberts suggested may contribute to the development of senile tricuspid aortic stenosis,[23] may also contribute to aortic valve calcification and to aortic stenosis in patients on long-term haemodialysis.

We also found that serum alkaline phosphatase and parathyroid hormone concentrations were increased in our patients with aortic stenosis, suggesting altered bone tissue metabolism and metastatic calcification as a probable cause of premature valve calcification. This accords with a report linking aortic sclerosis with renal osteodystrophy.[4] Nevertheless, the ranges for alkaline phosphatase and parathyroid hormone were too wide to predict the risk of aortic stenosis developing in individual patients with high serum concentrations. In addition, we used a C-terminal parathyroid hormone assay, which because it also measures the inactive metabolites of parathyroid hormone, is not very specific.

An increased calcium-phosphate product caused by secondary hyperparathyroidism and the failure to control hyperphosphataemia have been associated with premature calcification of the aortic valve and mitral annulus.[15 21 25] Maher *et al* found that the calcium-phosphate product was greater in patients with aortic calcification than in those without.[21] This finding contrasts with our patients who did not show a significant increase in the calcium-phosphate product despite the increase in parathyroid hormone concentrations. This discrepancy is not easy to explain but might be related to good control of phosphataemia in our patients, at least during the last 12 months on dialysis. Furthermore, others have reported similar findings to ours.[4]

The sensitivity of the clinical diagnosis of heart valve disease in the current study was low: 60% for aortic stenosis and 40% for mitral regurgitation. This accords with other studies.[13 22] Aortic stenosis was clinically diagnosed in only two out of five patients in a comparable study by Maher.[21] In a study by Labovitz 17 of 28 patients with known mitral regurgitation and calcification of the mitral annulus (out of a total of 51 patients with mitral annulus calcification) had an apical murmur. Of the 17 found to have a moderate to severe mitral regurgitation by Doppler, only 11 (65%) had a murmur consistent with mitral regurgitation. None of the four patients with Doppler echocardiographic evidence of mitral stenosis had a diastolic rumble or an opening snap.[22] Moreover, a systolic murmur may be caused by calcium in the mitral annulus itself (vibration of the mitral valve ring) independent of mitral regurgitation.[22] The clinical diagnosis of degenerative aortic stenosis in elderly patients is known to be difficult.[8 10] Maher noted that systolic murmurs are commonly attributed to flow murmurs and other signs of aortic stenosis may be masked by hypertension and increased cardiac output.[21] Selzer and Roberts proposed factors influencing clinical diagnosis such as a different configuration of a usually tricuspid valve, calcium deposits limited to the aortic aspects of the valve, unfused commisures, and additional calcification of the mitral annulus in most patients[10 13]: these causes may also be relevant in patients with end stage renal disease on long-term haemodialysis.

Conclusions

Degenerative calcification of the aortic and mitral valves was more common in patients with end stage renal failure on long-term haemodialysis than that reported in patients of similar age with normal renal function. Unlike patients with normal renal function and valve disease there was no preponderance of female patients: the association between calcification of the mitral annulus and aortic valve was equally common in both sexes. The proportion of patients on long-term haemodialysis with important disease of the aortic and mitral valves was much higher than would have been predicted by clinical examination. The duration of haemodialysis and altered bone metabolism may be aetiological factors in the development of aortic stenosis. Prevention or early treatment of secondary hyperparathyroidism might be important. Because aortic stenosis can progress rapidly[26 27] and can lead to severe hypotension during haemodialysis, Doppler echocardiography at regular intervals is recommended in order to assess haemodynamically important valve lesions, even in the absence of clear cardiovascular symptoms.

1 Maher ER, Pazianas M, Curtis JR. Calcific aortic stenosis: a complication of uremia. *Nephron* 1987;**47**:119–22.

2 Fulkerson PK, Baever BM, Auseon JC, Graber HL. Calcification of the mitral annulus. *Am J Med* 1979;**66**:967–77.

3 Forman MB, Virmani R, Robertson RM, Stone WJ. Mitral annular calcification in chronic renal failure. *Chest* 1984;**85**:367–71.

4 Nesser HJ, Baumgartner G, Danzer E, Davogg E, Watschinger B. Mitralringverkalkungen bei Dialysepatienten. *Dtsch Med Wochenschr* 1984;**109**:170–4.

5 Schott CR, Kotler MN, Parry WR, Segal BL. Mitral annular calcification: clinical and echocardiographic correlations. *Arch Intern Med* 1977;**137**:1143–50.

6 Roberts WC. Morphologic features of the normal and abnormal mitral valve. *Am J Cardiol* 1983;**51**:1005–28.

7 Ritschard T, Blumberg A, Jenzer HR. Mitralanulusverkalkungen bei Dialysepatienten. *Schweiz Med Wochenschr* 1987;**117**:1363–7.

8 Lombard JT, Selzer A. Valvular aortic stenosis: a clinical and hemodynamic profile of patients. *Ann Intern Med* 1987;**106**:292–8.

9 Maher ER, Curtis JR. Calcific aortic stenosis in patients with chronic renal failure. *Lancet* 1985;**ii**:1007.

10 Selzer A. Changing aspects of the natural history of valvular aortic stenosis. *N Engl J Med* 1987;**317**:91–8.

11 Bryg RJ, Gorden PR, Migdal SD. Doppler-detected tricuspid mitral or aortic regurgitation in end stage renal disease. *Am J Cardiol* 1989;**63**:750–3.

12 Nestico PF, Depace NL, Kotler MN, *et al*. Calcium phosphorus metabolism in patients with and without mitral anular calcium. *Am J Cardiol* 1983;**51**:497–500.

13 Roberts WC. The senile cardiac calcification syndrome. *Am J Cardiol* 1986;**58**:572–4.

14 Feigenbaum H. Calcified mitral anulus. In: Feigenbaum H, ed. *Echocardiography*. 4th ed. Philadelphia: Lea and Febiger, 1986:345–50.

15 Roberts WC, Waller BF. Effect of chronic hypercalcaemia on the heart: an analysis of 18 necropsy patients. *Am J Med* 1981;**71**:371–84.

16 D'Cruz I, Panetta F, Cohen H, Glick G. Submitral calcification or skelerosis in elderly patients: M-mode and two-dimensional echocardiography in "mitral anulus calcification". *Am J Cardiol* 1979;**44**:31–8.

17 Nestico RF, DePace NL, Morganroth J, Kotler MN, Ross J. Mitral anular calcification: clinical, pathophysiologic and echocardiographic review. *Am Heart J* 1984;**107**:989–96.

18 Pomerance A. Pathological and clinical study of calcification of the mitral valve ring. *J Clin Pathol* 1970;**3**:354–61.

19 Lewandowski BJ, Winsberg F. Incidence of aortic and mitral anulus calcification as determined by echocardiography: significance and interrelationship. *Am J Radiol* 1982;**138**:829–32.

20 Wren C, Petch MC. Calcific aortic stenosis. *J R Coll Physicians Lond* 1983;**17**:192–5.

21 Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR. Aortic and mitral valve calcifications in patients with end stage renal disease. *Lancet* 1987;**ii**:875–7.

22 Labovitz AJ, Nelson JG, Windhorst DM, Kennedy HL, Williams GA. Frequency of mitral valve dysfunction from mitral anular calcium as detected by Doppler echocardiography. *Am J Cardiol* 1985;**55**:133–7.

23 Roberts WC. The structure of the aortic valve in clinically isolated aortic stenosis: an autopsy study of 162 patients over 15 years of age. *Circulation* 1970;**42**:91–7.

24 Pomerance A. Pathogenesis of aortic stenosis and its relation to age. *Br Heart J* 1972;**34**:569–74.

25 Breadly JR, William PF, Evans DB. Aortic valve replacement in chronic renal failure. *Lancet* 1985;**ii**:1370.

26 Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol* 1989;**13**:545–50.

27 Roger VL, Tajik AJ, Bailey KR, Oh JK, Taylor CL, Seward JB. Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. *Am Heart J* 1990;**19**:331–8.

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Stenting of the arterial duct: a new approach to palliation for pulmonary atresia

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Abstract

Objective—To assess the possibility of maintaining ductal patency in neonates with complex pulmonary atresia by percutaneous implantation of balloon expandable stents.

Patients—Two duct-dependent neonates with long segment pulmonary atresia, right sided aortic arch, and left sided arterial duct.

Results—Stents with final diameter of 3·5 or 4 mm and initial length of 7 or 15 mm were successfully positioned in the arterial duct. Two stents were required in one child and four in the other in order to stent the entire length of the duct. After the procedures the ducts remained widely patent and arterial oxygen saturations remained above 80%. Complications of the procedures included perforation of a peripheral pulmonary artery and cardiac perforation, both caused by guide wire manipulation. Both babies died suddenly, one at five weeks, and the other at nine days after successful stenting of the duct. Both ducts were patent at necropsy; the exact cause of one death was not clearly defined, but the second seemed to be caused by pneumococcal septicaemia.

Conclusions—Stenting of the arterial duct is technically feasible. It provides adequate palliation for neonates with pulmonary atresia at least in the short term and it seems to result in balanced, central perfusion of both pulmonary arteries. This preliminary report suggests that this previously untried technique may prove to be a promising and attractive alternative to neonatal aortopulmonary shunt operation.

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Conventional palliative treatment of duct dependent long segment pulmonary atresia consists of treatment with prostaglandin E in the short term and of surgical fashioning of an aortopulmonary shunt in the medium term. A logical alternative to surgical aortopulmonary anastomosis would be to prevent the arterial duct from closing. Expandable metal stents have proved effective in the treatment of intravascular stenoses at various sites including the pulmonary arteries and the inferior caval vein[1] and, more recently, in coronary artery stenosis or intimal dissection after balloon angioplasty.[2] Stenting of the arterial duct in duct dependent congenital heart disease has not, however, been attempted. We report the successful maintenance of ductal patency by implantation of expandable stainless steel stents. The technical procedure (performed in each case under general anaesthesia), its potential complications, and its very considerable future promise in the palliation of duct dependent congenital heart disease are discussed.

Patients and methods

CASE 1

A 2·6 kg boy presented with cyanosis and a soft continuous murmur when he was four hours old. He had an extensive cleft lip and palate and a bifid right thumb. Echocardiography and later cardiac catheterisation and angiography showed severe hypoplasia of the right ventricle and tricuspid valve with an intact ventricular septum, right ventricular sinusoids, long segment pulmonary atresia, small but confluent pulmonary arteries, a right sided aortic arch, and a left sided arterial duct arising at the origin of the left subclavian artery. He was maintained on an infusion of prostaglandin E and at the age of five days underwent a Waterston aortopulmonary anastomosis. The right pulmonary artery was found to be approximately 2·5 mm in diameter behind the ascending aorta. Postoperatively the child remained duct dependent. Angiography showed that the shunt was completely occluded. In view of the failed attempt at surgical palliation and with informed consent from the child's parents, we believed the alternative approach of stenting the arterial duct was justified.

Initially we chose a titanium wire stent (William Cook, USA) that was premounted on a balloon catheter with 4 mm inflated diameter and a 5F shaft. The 6F sheath necessary for delivery of the device, however, proved too large to pass retrogradely up the femoral artery or anterogradely to the duct via the inferior caval vein, the atrial septum, the left ventricle and the ascending aorta. Clearly, it was essential to use a device that could be delivered through a smaller sheath and we then chose a Palmaz-Schatz stainless steel stent (Ethicon Ltd, Johnson & Johnson) designed for implantation in adult coronary arteries (fig 1).[1 2] This stent is 15 mm long, consisting of two 7 mm lengths joined by a single 1 mm bridge, the two halves being

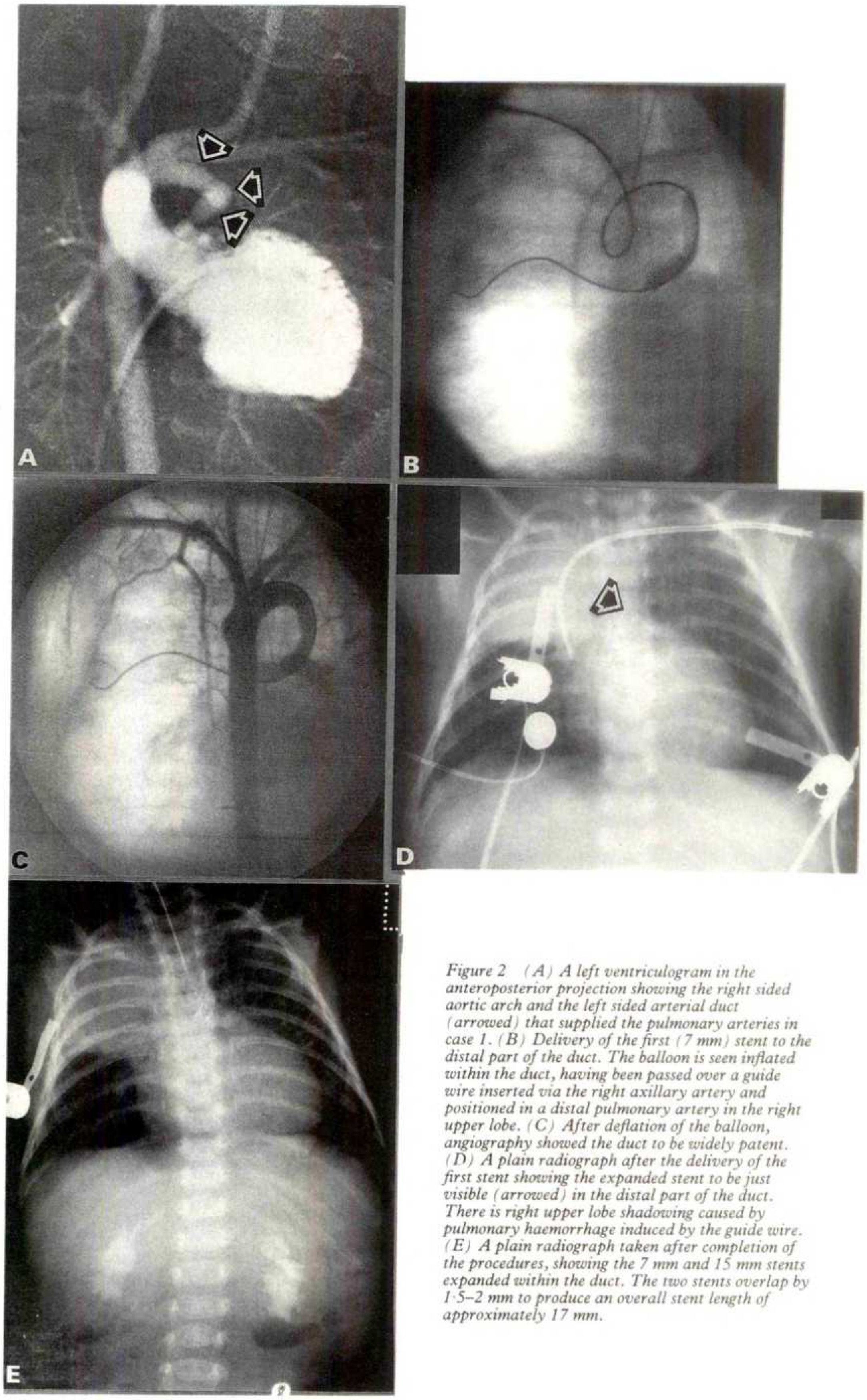

Figure 2 (A) A left ventriculogram in the anteroposterior projection showing the right sided aortic arch and the left sided arterial duct (arrowed) that supplied the pulmonary arteries in case 1. (B) Delivery of the first (7 mm) stent to the distal part of the duct. The balloon is seen inflated within the duct, having been passed over a guide wire inserted via the right axillary artery and positioned in a distal pulmonary artery in the right upper lobe. (C) After deflation of the balloon, angiography showed the duct to be widely patent. (D) A plain radiograph after the delivery of the first stent showing the expanded stent to be just visible (arrowed) in the distal part of the duct. There is right upper lobe shadowing caused by pulmonary haemorrhage induced by the guide wire. (E) A plain radiograph taken after completion of the procedures, showing the 7 mm and 15 mm stents expanded within the duct. The two stents overlap by 1·5–2 mm to produce an overall stent length of approximately 17 mm.

5 mg/kg in three divided doses daily. He was extubated 11 days later, when pulse oximetry showed stable oxygen saturations between 80% and 85%. Four weeks after the procedure he remained well saturated but mildly tachypnoeic, requiring treatment with diuretics. He was found dead in his cot when he was five weeks old. At necropsy the duct and both branch pulmonary arteries were widely patent and the immediate cause of death was uncertain.

CASE 2

A 2·6 kg boy presented with cyanosis when he

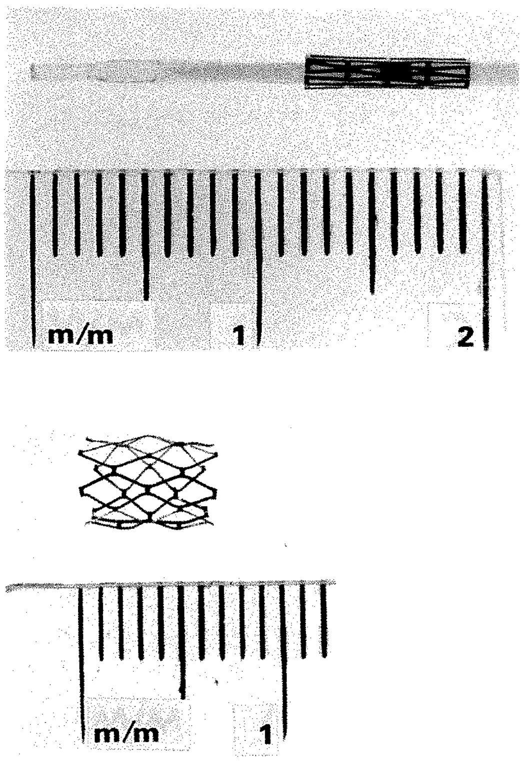

Figure 1 A 7 mm long Palmaz-Schatz coronary stent (A) unexpanded, mounted upon a 3·7F, 4 mm coronary angioplasty balloon catheter and (B) after inflation to a diameter of 4 mm.

easily separated into equal 7 mm lengths by very careful cutting of the bridge (although this is not recommended by the manufacturer). After inflation to 4 mm diameter the 7 mm length shortens to approximately 6 mm and the 15 mm long complete stent shortens to approximately 13 mm. The stent is operator mounted on a balloon catheter of the operator's choice, in this case an ACS coronary angioplasty balloon catheter with an inflated diameter of 4 mm and shaft of 3·7 F.

At right axillary artery cutdown a 5F Van Andel sheath (William Cook) was passed to the aortic arch. A 4F multipurpose catheter was passed through the sheath, bleeding being prevented by an ACS Tuohy-Borst type rotating haemostatic valve. A superfloppy 0·016 inch guide wire was manipulated down the duct and into the peripheral left lower lobe pulmonary artery. The catheter was then advanced over the guide wire into the distal pulmonary artery, the guide wire was exchanged for a stiffer wire (intermediate 0·016 inch, USCI Bard) and the multipurpose catheter was replaced by the balloon catheter with the stent mounted upon it. The balloon catheter was positioned (dye injected through the sheath and the central balloon marker were used to guide accurate placement) in the duct and the balloon was inflated to 4 mm at a pressure of 8 atm for 20 seconds. There was transient hypotension and a fall in oxygen saturation during balloon inflation, with prompt recovery after deflation. Repeat angiography showed the duct to be widely patent and pulse oximetry showed an increase in peripheral oxygen saturation from 75% to 90%. The stent was not visible on radiographic screening, but this was not considered remarkable because the stent is rarely visible in adult coronary arteries. Treatment with prostaglandin E was stopped and the arteriotomy repaired.

After three hours the oxygen saturation fell to 40%. This did not improve after thrombolytic treatment but rose again to 85% when intravenous prostaglandin was restarted. Doppler colour flow mapping showed evidence of distal ductal stenosis which suggested that the implanted stent was too short. An attempt at changing to oral prostaglandin was unsuccessful.

Ten days later a second right axillary arteriotomy was performed and a 7 mm Johnson & Johnson stent was positioned in a similar manner in the distal duct uneventfully using a similar 4 mm balloon catheter (fig 2). Angiography confirmed a very satisfactory stent position in the distal part of the duct, with the stent being just visible on screening and plainly visible on the plain chest radiograph on this occasion (fig 2). The duct was widely patent and the arterial oxygen saturation had again risen to 90%. The child was returned to the intensive care unit, where 15 minutes later the oxygen saturation again fell to 40%, there was a fresh haemorrhage from the endotracheal tube and radiographic evidence of right upper lobe consolidation. The bleeding stopped without specific treatment but the next day oxygen saturation had not improved. Thrombolytic treatment did not cause any further haemorrhage but failed to produce any clinical improvement and prostaglandin E had little effect in the dose previously used successfully. Ultrasound examination proved unhelpful on this occasion. A repeat chest radiograph, however, showed the distal stent clearly, but the longer stent was still not visible in the proximal duct or in any other position in the vascular system. Retrospectively it became clear that the first stent had not, in fact, been deployed in the duct and had been pushed backwards off the balloon during the introduction of the balloon catheter, later to be unwittingly discarded inside the haemostatic valve.

The child improved with high dose intravenous prostaglandin E. His parents encouraged us to reattempt stenting of the proximal duct, and three days later the child was returned to the catheter laboratory where, through a left axillary artery cutdown, a 15 mm stent was easily positioned and expanded to 4 mm in the proximal duct overlapping the distal stent by 1·5–2 mm. Repeat angiography showed the entire duct to be widely patent and both stents were visible on screening and on the plain chest radiograph (fig 2). The oxygen saturations remained above 85% without prostaglandin E. The child was treated with dipyridamole, aspirin, and a heparin infusion pending stabilisation of the prothrombin time on warfarin.

His recovery was complicated by a further pulmonary haemorrhage five days later, requiring reversal of anticoagulation with fresh frozen plasma and discontinuation of warfarin. He continued to be treated with aspirin 15 mg/kg once daily and dipyridamole was two days old. He was the second of twins (his twin brother had coarctation of the aorta). Investigation showed him to have atrial isomerism, a complete atrioventricular septal defect, and long segment pulmonary atresia with confluent but small pulmonary arteries and with a right sided aortic arch and a left sided arterial duct supplying the pulmonary arteries. His parents wished to avoid surgical treatment and gave their informed consent to an attempt at stenting the arterial duct. Angiography via a right axillary artery cutdown and a 5F Van Andel sheath confirmed a right sided aortic arch with a long, curved, distally stenosed duct arising from the left side of the proximal aortic arch. The left subclavian artery arose anomalously from the descending aorta. The arterial duct was cannulated with a 4F Cobra catheter, a 0·014 inch guide wire was positioned in the right lower lobe pulmonary artery, and a 7 mm long Johnson & Johnson stent was deployed in the distal duct through a 4 mm (3·3F) ACX coronary angioplasty balloon catheter. A brief attempt was made to insert a second stent more proximally in the duct, but the procedure was abandoned because of increasing metabolic acidosis and transient extreme bradycardia. The child made a prompt recovery. Treatment was continued with prostaglandin E, dipyridamole, and heparin.

Six days later the right femoral vein was catheterised and a 4F Cobra catheter was passed to the right atrium, the right ventricle, across the ventricular septal defect to the ascending aorta, and thence to the arterial duct. A guide wire (0·018 inch Terumo) was positioned in the right lower lobe pulmonary artery and the catheter was exchanged for a 3·5 mm (3·6F) ACS Pinkerton balloon angioplasty catheter. During catheter manipulation through the right ventricle the stent became dislodged distally from the balloon, coming to lie on the guide wire alone high in the inferior caval vein. The stent was retrieved by snaring the distal end of the guide wire in the right atrium via a second catheter in the femoral vein. Retrieval of the stent was complicated by acute tamponade caused by cardiac perforation by the tip of the snare, but this was treated successfully by prompt pericardiocentesis and autotransfusion. The procedure was abandoned. The child made an uncomplicated recovery and eight days later the duct was again catheterised with a 6F long curved sheath via the left femoral vein. The sheath was advanced to the ascending aorta and a guide wire was positioned in the right lower lobe pulmonary artery. A 15 mm stent was deployed in the duct with its tip just inside the existing 7 mm stent in the distal duct. Repeat angiography showed satisfactory stent positions with excellent flow to both pulmonary arteries, but the combined length of the stents still seemed to be too short. A further 7 mm stent was deployed in the most proximal part of the duct. Transient marked hypotension and bradycardia occurred at this stage, apparently owing to splinting of the right ventricle, the atrioventricular valve, and the aortic valve by the sheath. Final angiography showed a very satisfactory result.

Treatment was continued with dipyridamole, aspirin (15 mg/kg/day), and a heparin infusion to keep the activated partial thromboplastin time at 2–2·5 times the control value. The child remained well with arterial oxygen saturations above 80%. He was extubated the following day and anticoagulated with warfarin, our initial plan being to continue this for eight weeks, when we expected that endothelialisation of the stent would be complete.

Ten days later he again became cyanosed. Repeat aortography via the right femoral artery showed very localised stenosis of the duct immediately at its junction with the pulmonary artery (fig 3). A further 7 mm stent was delivered to this site and dilated to a diameter of 3·5 mm without difficulty, and with prompt improvement in oxygen saturation to 90%. At review eight days later the child was well and gaining weight. Pulse oximetry showed readings between 80% and 90% throughout the day. He was discharged home, where the following day he suffered two apnoeic episodes despite remaining pink and well. He suffered a further apnoeic episode on the way to hospital and resuscitation was unsuccessful. Necropsy showed that the duct was patent; there was asplenia and pneumococci were isolated from postmortem blood cultures. Three days later his twin brother was admitted to hospital after a near miss cot death at home.

Discussion

Although aortopulmonary shunt operations provide life-saving palliative treatment at low risk for neonates with pulmonary atresia, such surgical treatment has potential drawbacks. Both Blalock-Taussig (classical or modified) and Waterston shunts usually produce preferential blood flow to the pulmonary artery on the side of the shunt that can result in differential growth of the right and left pulmonary arteries. The Waterston anastomosis may be associated with distortion of the right pulmonary artery or pulmonary hypertension, and any kind of surgical intervention will inevitably result in scarring which may increase the risk of later, more definitive, surgical treatment. Non-surgical maintenance of ductal patency is therefore a highly desirable goal.

The recent development of stents for implantation into coronary arteries had led to the manufacture of stents of suitable size for use in the neonatal arterial duct. There are various forms of stent—from elaborate balloon expandable titanium coils to expandable stainless steel tubes and self expanding sprung steel cages. Self expanding stents have the potential disadvantage of relative lack of operator control of the final stent diameter. Balloon expandable stents have the theoretical advantage that it may prove possible to increase stent diameter at a later date simply by repeat balloon dilatation. We therefore thought that a balloon expandable stent was best suited to our purpose. Our initial choice of the Cook titanium coil design was prompted by the fact that the stent is clearly visible on radiographic screening. However, our experience suggests that a delivery system of 6F is too large to allow safe

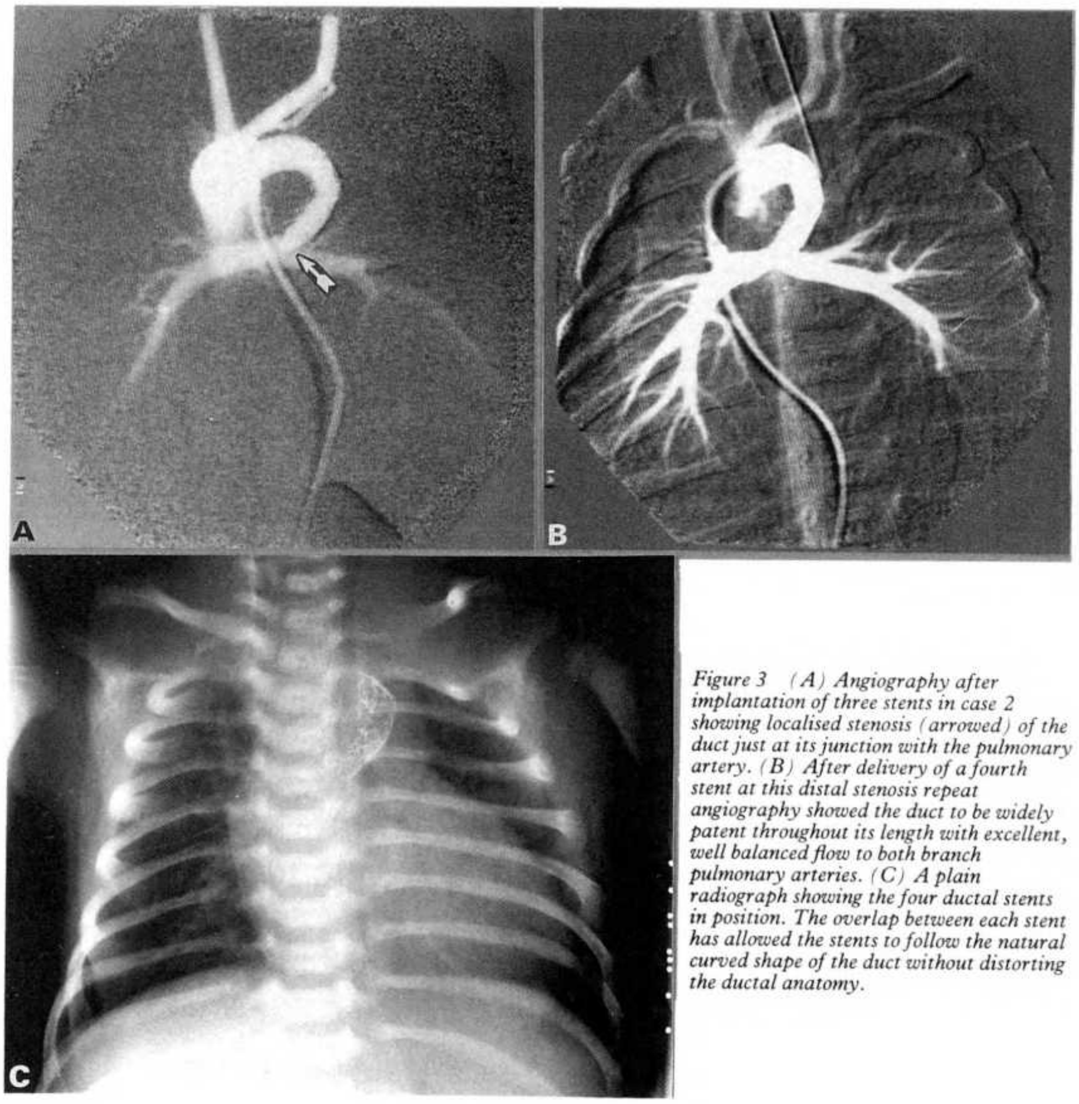

Figure 3 (A) Angiography after implantation of three stents in case 2 showing localised stenosis (arrowed) of the duct just at its junction with the pulmonary artery. (B) After delivery of a fourth stent at this distal stenosis repeat angiography showed the duct to be widely patent throughout its length with excellent, well balanced flow to both branch pulmonary arteries. (C) A plain radiograph showing the four ductal stents in position. The overlap between each stent has allowed the stents to follow the natural curved shape of the duct without distorting the ductal anatomy.

percutaneous arterial access in babies of this size. The Palmaz-Schatz stent has the distinct advantage of being operator mounted on the balloon catheter rather than being premounted by the manufacturer. This allows the operator to choose a balloon catheter of appropriate length, shaft size, and inflated diameter for individual ductal anatomy. The catheters we chose had shaft sizes of only 3·3, 3·6, and 3·7F and even with the stent mounted upon the balloon the catheter passed easily through a 5F sheath which, in turn, was small enough to be introduced into the axillary artery with ease.

Despite the repeated cardiac catheterisations required in these cases before successful stenting of the duct, we encountered few major complications. Arterial damage should be avoidable if the stent delivery system can be kept as small as 5F. A peripheral right pulmonary artery was perforated by a superfloppy wire and the tip of a snare fashioned from a 0·014 inch guide wire perforated the heart. Heightened awareness of the possibility that even atraumatic wires can perforate the heart or blood vessels should minimise this risk.

It seems likely that the pulmonary haemorrhage in our first case was exacerbated by antiplatelet and anticoagulant therapy and in our case the bleeding required warfarin treatment to be stopped. Despite this there has been no suggestion of clot formation within the stent and it may be that the high flow through a 4 mm diameter duct makes thrombosis unlikely and anticoagulant therapy unneccessary. Treatment with aspirin and dipyridamole does, however, seem advisable in the light of experience with stent implantation at other sites,[1 2] at least until the stent surfaces are likely to be completely endothelialised. We provisionally planned to continue these drugs for approximately two months from the stent implant. No complications were caused by ductal damage, although dissection of the duct by a guide wire or tears induced by stent deployment remain theoretical risks.

Repeated procedures were required in both our cases because short sections of the arterial duct remained unstented. This was partly because we decided to stent the ducts in sections, sometimes using half length stents to maximise flexibility of the balloon catheter/stent combination at tortuous sites. The most distal part of the duct seems to have remarkable powers to constrict even when only a few millimetres is left unstented. We now appreciate that great care has to be taken to ensure very accurate stent positioning at this end of the duct at an initial procedure if repeated visits to the catheter laboratory are to be avoided.

There was no clear cause of death in our first case, but as far as is possible to ascertain neither child died with inadequate pulmonary blood flow. The first child had apnoeic attacks in the immediate neonatal period which had been attributed to airway obstruction related to his extensive cleft palate and it is possible that this may have contributed to his death. His pulmonary blood flow seemed to be relatively high and he had required treatment with diuretics; left ventricular volume overload may also have contributed to his death. The second child had extremely complex congenital heart disease and asplenia. His death was almost certainly due to septicaemia, because pneumococci were grown from the postmortem blood culture. His twin brother's near miss cot death is also of note but of uncertain relevance. We are planning further detailed investigation of the ducts, including histological assessment of endothelialisation.

Further follow up and further experience in other patients with a wider variety of ductal anatomy is clearly required before medium term results of ductal stenting can be assessed. At least in the short term, however, this procedure seems to promise a non-surgical alternative to aortopulmonary shunt surgery, with the very attractive benefit of providing balanced perfusion of both lungs and therefore the potential of balanced growth of the pulmonary arteries.

1 Mullins CE, O'Laughlin MP, Vick GW, *et al.* Implantation of balloon expandable intravascular grafts by catheterisation in pulmonary arteries and systemic veins. *Circulation* 1988;77:188–99.
2 Schatz RA, Baim DS, Leon M, *et al.* Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation* 1991;83:148–61.

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Cardiac conduction abnormalities and rhythm changes after neonatal anatomical correction of transposition of the great arteries

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Abstract
Seventy three infants who underwent neonatal anatomical correction for transposition of the great arteries with or without a ventricular septal defect were reviewed for evidence of conduction and rhythm abnormalities on preoperative and postoperative 12 lead electrocardiograms and during 24 hour Holter monitoring. There was a partial right bundle branch block pattern in 47% (29/62) of all patients and in 60% (24/40) of those with simple transposition. Complete right bundle branch block was noted in 21% including 5% with simple transposition. Holter monitoring showed sinus rhythm in all patients except three: one had episodes of supraventricular tachycardia, another an intermittent second degree heart block, and a third a complete heart block. Atrial extrasystoles were noted in 47% (29/62) of patients but were frequent in only three patients. Occasional unifocal ventricular extrasystoles were encountered in 37% (23/62) of patients and were frequent in a further 3% (2/62). Only one patient (2%) developed multifocal ventricular extrasystoles. The frequency of important cardiac arrhythmias after neonatal anatomical correction of transposition of the great arteries was 5%, significantly less than that reported after atrial inflow diversion for the same malformation.

In the past decade anatomical correction has become the treatment of choice for simple transposition of the great arteries as well as for transposition with ventricular septal defect. Early concerns[1–3] included the ideal age for surgery, late ventricular function, neo-aortic valve competence, late coronary ostial stenosis, growth of the atrial anastomoses and the frequency of postoperative arrhythmias.[4 5] Many of these concerns have been allayed to a large extent,[6–8] though reports of pulmonary artery stenosis are not uncommon.[8–10] Normal ventricular function has been reported,[10–13] together with a low frequency of important arrhythmias in the postoperative period.[14–16]

These earlier studies of rhythm disturbances included a heterogenous group where the anatomical correction was done usually later in infancy after earlier banding of the pulmonary artery.[14 15] In a subsequent study 54 of the 92 patients reviewed had a primary (1 stage) anatomical correction, but 23 of the 29 who had their ventricular septal defect closed required a ventriculotomy.[16] Neonatal arterial switches including closure of a ventricular septal defect without the need for a ventriculotomy have been successfully performed at this centre since 1983.[7] Such patients formed a homogeneous group subjected to early correction and in whom conduction and rhythm disturbances could be studied before (whenever such information was available) and after operation.

Patients and methods

We studied all patients who had transposition of the great vessels or transposition with a ventricular septal defect and who had correction in the neonatal period and were subsequently followed up at our hospital. The former group also included infants with a small ventricular septal defect that did not require closure. We excluded patients with "complex" transposition—for example double outlet right ventricle or those with multiple ventricular septal defects. We also excluded the few infants who had surgery beyond the neonatal period or those who had an initial pulmonary artery banding done before anatomical correction. None of the patients had a ventriculotomy for closure of a ventricular septal defect. We also excluded patients returning overseas, or leaving the state, or lost to follow up.

The records of each infant were reviewed and any preoperative or postoperative risk factors that might predispose to an arrhythmia were noted. Special attention was given to the coronary artery patterns as well as any difficulties encountered in their transfer. At follow up (mean duration 27 months and up to 68 months) the clinical, cross sectional echocardiographic, and cardiac catheterisation findings were noted. All available preoperative (before and after balloon atrial septostomy), postoperative, and serial follow up electrocardiograms were reviewed. After the study started a sample group of patients underwent 24 hour Holter monitoring preoperatively and in the immediate postoperative period for the purpose of comparison. Subsequent 24 hour Holter recordings were obtained after admission for postoperative cardiac catheterisation, at review appointments, or after letters of recall. All such Holter monitoring was carried

Table 1 Clinical details

Data	Anatomy Simple TGA	 TGA with VSD	 Total
Patients	49	24	73
Age at switch (days):			
Range	3–28	8–28	3–28
Mean	12	15	
Follow up (mnth) (range)	2–63	2–68	2–68
Holter recordings:			
Preoperative (n)	13	3	16
Postoperative (n)	13	4	17
Follow up	37	23	60
Range (mean) (mnth)	5–60 (26)	2–68 (29)	2–68 (27)

TGA, transposition of the great arteries; VSD, ventricular septal defect.

out when the subject was off medical treatment except for one who was taking digoxin for supraventricular tachycardia. All the electrocardiograms were examined for any conduction abnormalities or arrhythmia. The Texas Children's Hospital Pediatric Electrocardiographic norms were used in interpretation,[17] and all abnormal findings were tabulated. The Holter recordings were reported by an experienced cardiac technician (CS) and hard copies of any arrhythmias were reviewed by the cardiologist. Like Martin *et al*[16] short periods of sinus bradycardia (over 50/minute) or of sinus tachycardia (under 180/minute) were accepted as being within normal limits, as was sinus arrhythmia or brief sinus pauses.[18-23] Right bundle branch block was diagnosed when a typical rsR pattern was seen in V1 and V2 associated with broad S waves in V6 and when the QRS duration was above the upper limit for age. A similar pattern with a normal QRS interval was diagnosed as partial right bundle branch block. Less than 12 supraventricular extrasystoles per peak hour were classified as being occasional and more than 12 per peak hour as frequent. Supraventricular tachycardia was diagnosed when it occurred for more than three beats in succession. Ventricular arrhythmias were classified according to the modified Lown criteria.[16]

Results

Seventy three patients who had a neonatal arterial switch operation and who satisfied the above selection criteria were included in the study group. Forty nine had simple transposition and 24 had transposition with ventricular septal defect requiring closure. All patients had a balloon atrial septostomy at presentation. Table 1 summarises their clinical details. Fifty three per cent (39 neonates) had surgery in the first two weeks of life. There was difficulty in transferring the coronary arteries in four patients. In two the infundibular branch had to be sacrificed, while the other two needed stay sutures or reimplantation of the coronary artery because of kinking of the right coronary artery.

Tables 2 and 3 summarise the details of the electrocardiograms and Holter traces: not all the infants had preoperative electrocardiograms. Preoperative and immediate postoperative (first two weeks) 24 hour Holter recordings were available from 16 and 17 patients respectively.

ELECTROCARDIOGRAPHIC FINDINGS

Two patients had transient evidence of myocardial ischaemia in the postoperative period. Thirteen others (18%) had non-specific ST segment or T wave changes in the electrocardiogram recorded immediately after operation.[15] At follow up none of the patients had persistent evidence of ischaemia or any ST segment or T wave changes. Ischaemic changes did not develop in any of the patients in whom there was difficulty in transfer of the coronary arteries.

Partial right bundle branch block, seen in 7% of patients preoperatively (five out of 64 who had a preoperative electrocardiogram) and at follow up in 47% (29/62), was the commonest "conduction" abnormality noted. Complete right bundle branch block was not seen preoperatively but was found in 21% (13/62) postoperatively. Two patients with simple transposition who developed right bundle branch block postoperatively had only a partial right bundle branch block at later follow up. Two others with simple transposition who in the immediate postoperative period had only a partial right bundle branch block went on to develop a complete right bundle branch block. All other patients with complete right bundle branch block had a ventricular septal defect closed. A partial right bundle branch block pattern disappeared in three patients. Right bundle branch block with left axis deviation was seen in 5% (3/62) of patients at follow up.

First degree heart block was seen in 5% (3/62) of patients, while one patient displayed intermittent second degree Wenckebach atrioventricular block on late follow up.

Table 2 Preoperative and postoperative electrocardiographic abnormalities

Patients	Simple transposition (n) (%) Pre BAS (43/49)	 Post BAS (45/49)	 Post op (49/49)	 Follow up (40/49)	Transposition with VSD (n) (%) Pre BAS (21/24)	 Post BAS (21/24)	 Post op (23/24)	 Follow up (22/24)	All cases Follow up (n) (%) (62/73)
Partial RBBB	4 (9)	4 (9)	34 (69)	24 (60)	1 (5)	0	6 (25)	5 (23)	29 (47)
Complete BBB	0	0	2 (4)	2 (5)	0	0	11 (48)	11 (50)	13 (21)
Left axis deviation	1 (2)	1 (2)	2 (4)	1 (3)	2 (9)	3 (16)	1 (4)	1 (5)	2 (3)
LAD + RBBB	0	0	0	0	0	0	3 (13)	3 (14)	3 (5)
I° heart block	0	0	0	3 (13)	0	0	0	0	3 (5)
II° heart block	0	0	0	0	0	0	0	1 (4)	1 (2)
Complete heart block	0	0	0	0	0	0	1 (4)	1 (4)	1 (2)
Non-specific ST/T wave changes	2 (4)	1 (2)	9 (18)	0	1 (5)	1 (5)	4 (17)	0	0
Ischaemia	0	0	0	0	0	0	2 (8)	0	0

RBBB, right bundle branch block; LAD, left axis deviation; ST/T wave changes, ST segment or T wave changes; BAS, balloon atrial septostomy; I°, first degree, II°, second degree.

Table 3 24 hour Holter monitoring: preoperative and postoperative arrhythmias

	Simple transposition (n) (%)			*Transposition with VSD (n) (%)*			*All cases at follow up (n) (%) 62*
	Pre op 13	*Post op 13*	*Follow up 39*	*Pre op 3*	*Post op 4*	*Follow up 25*	
SVE (occasional)	1 (8)	9 (69)	17 (43)	1 (33)	3 (75)	9 (38)	26 (42)
SVE (frequent)	1 (8)	0	3 (8)	0	0	0	3 (5)
Sinus slowing with SVE/JE	3 (23)	1 (8)	5 (13)	0	0	2 (8)	7 (11)
SVT	1 (8)	1 (8)	1 (3)	0	0	0	1 (2)
Junctional tachycardia	0	1 (8)	0	0	0	0	0
Ventricular arrhythmia:							
Grade I	5 (38)	5 (38)	14 (36)	2 (66)	1 (25)	9 (38)	23 (37)
Grade II	1 (8)	2 (16)	2 (5)	0	0	0	2 (3)
Grade III	1 (8)	1 (8)	1 (3)	0	1 (25)	0	1 (2)
Grade IV	0	0	0	0	0	0	0
Grade V	0	1 (8)	0	0	0	0	0

SVE, supraventricular extrasystoles; occasional, less than 12 beats in a peak hour; frequent, over 12 per peak hour; SVT, supraventricular tachycardia; JE, junctional extrasystoles.

Another infant with transposition and ventricular septal defect developed complete heart block after surgical correction.

HOLTER MONITORING

Preoperatively one neonate had supraventricular tachycardia, soon after balloon atrial septostomy. Follow up electrocardiograms and Holter recordings from this symptom free child showed sinus rhythm. A further patient with supraventricular tachycardia in the immediate postoperative period also had sinus rhythm on follow up two years after surgery. In another patient symptomatic supraventricular tachycardia at follow up (1/62, 2%) was controlled by digoxin; subsequent Holter recording two years after surgery showed sinus rhythm. Apart from the patient who developed postoperative complete heart block and another with intermittent Wenckebach block all others remained in sinus rhythm. However, seven (11%) patients at follow up showed brief sinus pauses with atrial or junctional escape beats. Two others had P waves with two different configurations on Holter recordings.

Isolated supraventricular extrasystoles were seen in 42% (26/62) of patients (rate of less than 12 beats per peak hour) on follow up. In a further 5% (3/62) of patients more frequent supraventricular extrasystoles were noted (over 12 beats per peak hour). There was a significant increase in the incidence of supraventricular extrasystoles at follow up compared with the preoperative sample group[16] ($p = 0{\cdot}003$).

At follow up, isolated ventricular extrasystoles (Lown grade I) were seen in 37% (23/62) of patients. However, in all but five of these there were fewer than five ventricular extrasystoles per trace. Two patients (5%) with simple transposition had Lown grade II ventricular arrhythmia, while only one patient (2%) showed infrequent multifocal ventricular extrasystoles (Lown grade III) on a follow up Holter recording. Lown grade IV and V ventricular arrhythmias were not seen. However, in the immediate postoperative period, one patient with simple transposition developed asymptomatic intermittent junctional tachycardia as well as intermittent ventricular tachycardia. He was briefly treated with oral amiodarone; a subsequent Holter recording showed sinus rhythm.

There was no correlation between arrhythmia and residual haemodynamic lesions. There was also no correlation with the coronary artery patterns. Two patients who had the infundibular branch sacrificed at surgery had normal Holter recordings and electrocardiograms at follow up, apart from a partial right bundle branch block. Another who required reimplantation of the right coronary artery also had a normal electrocardiogram and Holter recording on follow up. The second patient with right coronary transfer problems, however, developed infrequent multifocal ventricular extrasystoles on Holter recording, with partial right bundle branch block.

Discussion

A variable incidence of important cardiac arrhythmias has been reported after the Mustard and the Senning operations with the risk of late death associated with arrhythmia.[24] Holter studies on patients after such surgery suggested an incidence of 30–70% of important cardiac arrhythmias.[24-32] Junctional rhythm was the commonest abnormality noted. Several mechanisms have been proposed to explain this high incidence of arrhythmia. Initial reports prompted the suggestion that the high incidence of arrhythmia was inherent in transposition of the great vessels.[24] This assumption, however, has not been substantiated. Moreover, modifications of the Mustard and the Senning procedures have substantially reduced the incidence of arrhythmia. In addition preoperative Holter studies on patients with transposition of the great vessels,[14 16 28] including our sample group, have shown an incidence of arrhythmias similar to that seen in normal healthy infants and children,[18-23] though one of our patients developed supraventricular tachycardia soon after balloon atrial septostomy.

Previous studies reporting arrhythmias after the arterial switch operation have included diverse groups of patients who had either a primary arterial switch or arterial switch after initial pulmonary artery banding. They also included patients who had ventriculotomies for closure of a ventricular septal defect at various ages.[14-16] Nevertheless, arrhythmia was uncommon after operation and its frequency was not increased when surgery was carried out as a two stage procedure (after initial pulmonary artery banding) or when closure of a ventricular septal defect required a ventriculotomy.[16] The only patients in whom complete heart block developed had had closure of a Blalock-Hanlon septectomy.[14 16]

In this homogenous group of 73 neonates who had arterial switches we confirmed that postoperative conduction and rhythm disturbances were not common, even after closure of a ventricular septal defect. Only one infant developed a supraventricular tachycardia, which was well controlled by digoxin; an asymptomatic complete heart block developed in a second patient; and an intermittent Wenckebach block in a third. Martin *et al* also noted an increased incidence of supraventricular extrasystoles.[16] This low incidence of important arrhythmias may reflect the safety of the procedure in skilled hands and the early age (most by two weeks) at which the correction was carried out: this latter factor was also suggested by others.[16] The Mustard and Senning inflow diversions that are generally done in older infants and children are more likely to damage the sinus node or its blood supply,[27] to interrupt "specialised" atrial conduction tissue or the atrioventricular node, and thus to contribute to sudden death.[14]

Partial and complete right bundle branch block have been reported after anatomical correction, even in patients with an intact ventricular septum.[15] The occurrence of complete right bundle branch block after operation in two (4%) of our patients with simple transposition was unexplained. Both lacked evidence of myocardial ischaemia and had uncomplicated postoperative courses. None of our patients developed evidence of myocardial infarction or persistent ishaemia on the electrocardiogram or Holter trace at the last follow up (mean 27 months). There was no correlation between arrhythmia and residual haemodynamic lesions or between arrhythmia and coronary artery patterns. The two patients who had an infundibular branch sacrificed at surgery and a patient with right coronary artery transfer problems were in sinus rhythm and had partial right bundle branch block. Partial right bundle branch block is a normal finding in about 7% of children over the age of six months. A second patient with right coronary artery transfer problems developed infrequent multifocal ventricular extrasystyoles (Lown grade III) on follow up Holter monitoring.

Though some dispute that the risk of death associated with late arrhythmia is increased after atrial inflow diversion procedures[31] the higher incidence of important arrhythmias after such surgery has been well documented. Our study confirms earlier reports of a low incidence of such arrhythmias after neonatal anatomical correction and the lack of persistent ischaemic changes in the short and medium term follow up. These findings indicate that neonatal correction has additional advantages over the Mustard and Senning procedures.

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1 Williams WG, Freedom RM, Culham G, *et al.* Early experience with arterial repair of transposition. *Ann Thorac Surg* 1981;32:8–15.
2 Stark J. Transposition of the great arteries: Which operation? *Ann Thorac Surg* 1984;38:429–31.
3 Oldham HN Jr. Arterial repair of transposition. *Ann Thorac Surg* 1981;32:1–3.
4 Flemming WH. Why switch? *J Thorac Cardiovasc Surg* 1979;78:1–2.
5 Zannine L, Lecompte Y, Jarreau MM, Hazan E. Transposition of the great arteries with ventricular septal defect: analysis of a series of 30 patients. *Pediatr Cardiol* 1983;4(suppl I):109–14.
6 Yacoub MH, Bernhard A, Radley-Smith R, *et al.* Supravalvarpulmonary stenosis after anatomic correction of transposition of the great arteries: causes and prevention. *Circulation* 1982;66(suppl I):193–7.
7 Brawn WJ, Mee RBB. Early results of anatomic correction of transposition of the great arteries and for double outlet right ventricle with subpulmonary ventricular septal defect. *J Thorac Cardiovasc Surg* 1988;95:230–8.
8 Okuda M, Nakazawa M, Imai Y, *et al.* Comparison of ventricular function after Senning and Jatene procedures for transposition of the great arteries. *Am J Cardiol* 1985;55:530–4.
9 Sievers HH, Lange PE, Onnasch DG, *et al.* Influence of two stage anatomic correction of simple transposition of the great arteries on left ventricular function. *Am J Cardiol* 1985;56:514–9.
10 Borow KM, Arensman FW, Webb C, Radley Smith R, Yacoub MH. Assessment of left ventricular contractile state after anatomic correction of transposition of the great arteries. *Circulation* 1984;69:106–12.
11 Vogel M, Benson LN, Smallhorn JF, *et al.* Catheter assessment of left ventricular function after arterial switch operation at rest and afterload stress [abstract]. *J Am Coll Cardiol* 1988;11:29A.
12 Sandor GS, Freedom RM, Williams WG, *et al.* Left ventricular systolic and diastolic function after two stage anatomic correction of transposition of the great arteries. *Am Heart J* 1988;115:1257–62.
13 Arensman FW, Radley-Smith R, Yacoub MH, *et al.* Catheter evaluation of left ventricular shape and function one or more years after anatomic correction of transposition of the great arteries. *Am J Cardiol* 1983;52:1079–83.
14 Arensman FW, Bostock J, Radley-Smith R, Yacoub MH. Cardiac rhythm and conduction before and after anatomic correction of transposition of the great arteries. *Am J Cardiol* 1983;52:836–9.
15 Lange PE, Pulse W, Sievers HH, *et al.* Cardiac rhythm and conduction after two-stage anatomic correction of simple transposition of the great arteries. *Thorac Cardiovasc Surg* 1986;34:22–4.
16 Martin RP, Radley-Smith R, Yacoub MH. Arrhythmias before and after anatomic correction of transposition of the great arteries. *J Am Coll Cardiol* 1987;10:200–4.
17 Gillette PC, Garson A, eds. Texas Children's Hospital electrographic criteria: normal values in pediatric cardiac dysrhythmias. New York: Grune and Stratton, 1981: 452–3.
18 Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PGB, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. *Br Heart J* 1980;43:14–20.
19 Southall DP, Orrell MJ, Talbot JF, *et al.* Study of cardiac arrhythmias and other forms of conduction abnormality in newborn infants. *BMJ* 1977;ii:597–9.
20 Southall DP, Johnston F, Shinebourne EA, Johnston PGB. 24-hour electrocardiographic study of heart rate and rhythm patterns in population of healthy children. *Br Heart J* 1981;45:281–91.
21 Montague TJ, Taylor PG, Stockton R, Roy DL, Smith ER. The spectrum of cardiac rate and rhythm in normal newborns. *Pediatr Cardiol* 1982;2:33–8.
22 Nagashima M, Matsushima M, Ogawa A, *et al.* Cardiac arrhythmias in healthy children revealed by 24 hour ambulatory ECG monitoring. *Pediatr Cardiol* 1987;8:103–8.
23 Valimaki I. Tape recordings of the electrocardiograms in newborn infants, Section II. Long term ECG tape recordings of newborn infants. *Acta Paediatr Scand* 1971; 75:(suppl I):169–75.
24 Southall DP, Keeton BR, Leanage R, *et al.* Cardiac rhythm and conduction before and after Mustard's operation for complete transposition of the great arteries. *Br Heart J* 1980;43:21–30.
25 Clarkson PM, Barratt-Boyes BM, Neutze JM. Late dysrhythmias and disturbances of conduction following Mustards operation for complete transposition of the great arteries. *Circulation* 1976;53:519–24.
26 Saalouke MG, Rios J, Perry LW, Shapiro SR, Scott LP. Electrophysiologic studies after Mustard's operation for d-transposition of the great vessels. *Am J Cardiol* 1978;41:1104–9.
27 Gillette PC, Kugler JD, Garson A Jr, *et al.* Mechanisms of cardiac arrhythmias after the Mustard operation for transposition of the great arteries. *Am J Cardiol* 1980;45:1225–30.
28 Martin TC, Smith L, Hernandez A, Weldon CS. Dysrhythmias following the Senning operation for transposition of the great arteries. *J Thorac Cardiovasc Surg* 1983;85: 928–32.
29 Beerman LB, Neches WH, Fricker FH, *et al.* Arrhythmias in transposition of the great arteries after the Mustard operation. *Am J Cardiol* 1983;51:1530–4.
30 Flinn CJ, Wolff GS, Dick M, *et al.* Cardiac rhythm after Mustard's operation for complete transposition of the great arteries. *N Engl J Med* 1984;310:1635–8.
31 Deanfield J, Camm J, Macartney F, *et al.* Arrhythmia and late mortality after Mustard and Senning operation for transposition of the great arteries. An eight-year prospective study. *J Thorac Cardiovasc Surg* 1988;96:569–76.
32 Williams WG, Trusler GA, Kirklin JW, *et al.* Early and late results of a protocol for simple transposition leading to an atrial switch (Mustard) repair. *J Thorac Cardiovasc Surg* 1988;95:717–26.

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RESUSCITATION

Potential impact of emergency intervention on sudden deaths from coronary heart disease in Glasgow

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Abstract

***Objective*—To determine the potential impact of emergency intervention strategies to prevent deaths from coronary heart disease outside hospital.**

***Design*—Analysis of routine medical and legal records of all persons dying of coronary heart disease in a defined population.**

***Setting*—Glasgow City, north of the river Clyde, 1984.**

***Subjects*—420 people under 65 years for whom the underlying cause of death on the death certificate was coronary heart disease (ICD 410–414, 9th Revision).**

***Results*—Of the 296 deaths outside hospital, 73% occurred at home. The deaths of 40% of those who died outside hospital were not witnessed and these people could not have received prompt cardiopulmonary resuscitation. Only 16% of the witnesses of a death attempted cardiopulmonary resuscitation before the arrival of a doctor or an ambulance crew. Over half (53%) of the cases in which cardiopulmonary resuscitation could have been attempted by a witness, but was not attempted, death occurred in the presence of the spouse or other close relative. Death occurred in the presence of a duty doctor or the ambulance crew in a maximum of 5% of deaths outside hospital. Ninety one per cent of people were dead before a call for help was made.**

***Conclusion*—Unless a greater proportion of patients receive cardiopulmonary resuscitation before emergency staff arrive at the scene the provision of emergency care staff with defibrillators is unlikely to have a significant impact on deaths outside hospital caused by coronary heart disease.**

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Most coronary deaths occur outside hospital.[1 2] Strategies to reduce the number of deaths include the provision of ambulance crews with defibrillators and education of the public in techniques of cardiopulmonary resuscitation. The likely impact of these strategies on coronary mortality outside hospital has not been assessed. In March 1989, the House of Commons Public Accounts Committee reported that there were no reliable data on the place and timing of coronary deaths in the community or the number of deaths that occur in the presence of ambulance crews or shortly before their arrival.[3] This study uses data from the Glasgow MONICA Project to assess the potential impact of these strategies to reduce coronary mortality outside hospital. The data are those for 1984, before any such developments had been introduced in Glasgow.

Patients and methods

The study was set in Glasgow, north of the river Clyde (table 1) in an area that is almost half of the city. It was based on 420 deaths in residents under 65 years of age occurring in 1984 for which the underlying cause of death on the death certificate was coronary heart disease (codes 410–414, International Classification of Diseases, 9th Revision). Data for 1984 from 32 other centres participating in the World Health Organisation (WHO) MONICA Project showed that Glasgow north of the Clyde had the fourth highest coronary mortality for men and the highest rate for women.[4]

We investigated each case in order to determine:

(*a*) The available clinical data in support of the diagnosis made at death, including symptoms, electrocardiograph and cardiac enzyme results, previous medical history, and necropsy findings.[5]

(*b*) The time and place of death, defined as the time and the place where irreversible cardiac arrest occurred.

(*c*) Whether the death was witnessed and by whom.

(*d*) Whether cardiopulmonary resuscitation was attempted and by whom.

Table 1 Study population: Glasgow, north of the River Clyde, 25–64 years old (1981 Census)

	Glasgow City	*Glasgow, north of the Clyde*
Men	153 246	95 600
Women	181 437	102 600
Total	334 683	198 200

(*e*) The medical and legal personnel who were involved after death had occurred.

(*f*) Whether there had been contact with a medical practitioner in the 28 days preceding death.

There were three main sources of information. The records of the Glasgow Death Unit were reviewed for all deaths, in order to determine which cases had been referred for medicolegal investigation. This unit is an office of the procurator fiscal, who is equivalent to a coroner in England and Wales. The records describe the circumstances of the death and the previous medical history as recorded by the police after interviews with relatives, witnesses of the death, and the general practitioner of the dead person. Interviews with witnesses of the fatal event are not carried out directly by Glasgow MONICA Project staff. High quality information is collected for the routine reports of the procurator fiscal.

To distinguish the deaths that occurred in hospital from those in people who were dead on arrival (and who were therefore not admitted) hospital case notes and the records of accident and emergency departments were examined for all cases in which a hospital was recorded on the death certificate as the place of death. Similar enquiries were made of appropriate medical and legal departments if death occurred outside Glasgow.

If the details of the circumstances of death and previous medical history could not be obtained from these sources, the information was obtained by sending a reply paid questionnaire to the general practitioner or by reviewing the general practitioner's clinical records after they had been returned to the primary care department of Greater Glasgow Health Board.

The validity of death certificate diagnoses was assessed on the basis of WHO MONICA diagnostic criteria for myocardial infarction and coronary death.[6] The category of "definite" depends on specified combinations of symptoms, and electrocardiographic, cardiac enzyme, or necropsy findings of cardiac infarction or coronary thrombosis. "Possible" cases are those in which the individual had suggestive symptoms or a previous history of coronary heart disease or necropsy evidence of chronic heart disease and no competing pathology to explain the death. Other categories are "insufficient data" where nothing relevant is known or "no myocardial infarction" when the symptoms and history are inappropriate or there is evidence of another pathology to explain the death.

Results

ASCERTAINMENT OF DATA

Information was obtained from at least one source for 419 of the 420 cases.

Two hundred and thirty one police reports were obtained for deaths that occurred outside hospital (including 103 cases that proceeded to a forensic necropsy examination). In one case, which the general practitioner said had been reported to the procurator fiscal, the report could not be found.

Completed questionnaires or records from general practitioners were obtained for 64 of 65 who died outside hospital and whose cases were not referred to the procurator fiscal.

Hospital case notes and electrocardiograms were reviewed for 16 cases: 11 of these received inpatient care in the 28 days before death and subsequently died outside hospital; one patient, who died before arrival at hospital, was admitted direct to a coronary care unit for cardiopulmonary resuscitation lasting two hours; two attended an accident and emergency department during the week before death; one attended an outpatient department 11 days before death, and another was visited at home by a hospital consultant on the day before death.

The records of the accident and emergency department were obtained for only four of the 10 who were dead on arrival at hospital and who were known (from the reports of the procurator fiscal) to have received cardiopulmonary resuscitation.

VALIDITY OF THE DIAGNOSIS

Three hundred and sixty three cases (86%) met the WHO MONICA criteria for "definite" or "possible" myocardial infarction or coronary death, a similar finding to that reported from a comparable study in Belfast.[7]

Seventeen cases (4%) were classified "no myocardial infarction" on the basis of clinical or pathological evidence of an alternative cause of death.

Forty cases (10%) were categorised as "unknown", because there were insufficient data to ascribe a "definite" or "possible" diagnosis. In only four of these were relevant documents not obtained. For 26 the records were obtained, but information on symptoms before death had not been recorded. In 10 relevant records were obtained and the information recorded was complete, but the information did not meet the criteria for a "definite" or "possible" diagnosis.

These findings indicate that the high coronary mortality in Glasgow is not explained by a high proportion of false positive cases. Because the purpose of the study was to assess the potential impact of preventive strategies on published coronary mortality data, all cases were included in subsequent analyses.

PLACE OF DEATH

One hundred and twenty three deaths (30%) occurred in hospital. One hundred and fifteen people died in hospital wards or departments, including two hospital staff at their place of work. Eight people died in accident and emergency departments. The main analyses are based on the 296 deaths (70%) that occurred outside hospital. They include 90 cases which were dead on arrival at hospital.

OUT OF HOSPITAL DEATHS

There were 215 (73%) deaths at home. Fourteen people died at another private address (for example, the home of a relative), 43 in a public place (for example, a social club), 13 died at

Table 2 Calls for medical help made before death for people with and without symptoms of coronary heart disease

	No symptoms (%)	*Symptoms (%)*	*Unknown symptoms (%)*	*Total (%)*
Called before death	0	22 (11)	4 (10)	26 (9)
Called after death	52	182 (89)	36 (90)	270 (91)
Total	52 (18)	204 (69)	40 (13)	296

Table 3 Arrival of general practitioners, ambulance crews, and the police before and after death occurred

	GP	*Ambulance*	*Police*	*Hospital*	*Other*	*NK*	*Total*
Attended before death	4	4					8
Attended after death	103	103	52	3	4	15	280
When attended unknown		8					8
Total	107	115	52	3	4	15	296

GP, general practitioner; NK, not known.

work, and five in an ambulance travelling to hospital. Three deaths occurred during transport to hospital in a taxi, a police car, and a private car. For three deaths outside hospital it was not possible to determine the exact place of death.

PREVIOUS ILLNESS

One hundred and twenty four people (42%) who died outside hospital had a previous history of coronary heart disease—72 of them had a previous myocardial infarction and 52 a history of angina.

Forty three (15%) had received medical care in the 28 days before death: 13 were hospital inpatients, 22 were seen by their general practitioner or a deputising doctor, three attended an accident and emergency department, three attended an outpatient department, and two were visited at home by a hospital consultant.

CALL FOR MEDICAL HELP

Only 26 people (9%) (table 2) called for help before they died and eight were visited by a medical practitioner or by the ambulance service (table 3). Three of these deaths occurred at home with the general practitioner in attendance, and five occurred in an ambulance travelling to hospital. In one case the general practitioner was accompanying the patient. Ten deaths occurred before medical help arrived, and in the remaining eight cases it was not possible to determine when death occurred in relation to the arrival of medical help.

SURVIVAL

The available data do not permit precise estimation of survival times, but at least 140 people (47%) are known to have died within an hour of the onset of acute symptoms (table 4). Fifty two deaths were sudden (that is, they were not preceded by reported symptoms), 56 occurred within 10 minutes and another 32 occurred within an hour of the onset of acute symptoms. A further 92 (32%) people were known to have survived less than 24 hours and 24 (8%) survived more than 24 hours. In the remaining 40 (14%) the duration of symptoms before death was not known. There was no difference in the pattern of survival between those with and without a previous medical history of myocardial infarction.

ARRIVAL OF HELP

Ambulance crews were first to arrive in 115 cases and general practitioners were first to arrive in 107 cases. All but 16 deaths occurred before the call for help was made. Two deaths at work and one at a football stadium were attended first by a medically qualified bystander. Another was first attended by a district nurse, and three other deaths were first confirmed by a hospital casualty doctor. The police were first to arrive in 52 cases. In the remaining 15 cases it was not possible to determine who first attended after death.

CARDIOPULMONARY RESUSCITATION

One hundred and nineteen deaths (40%) were unwitnessed (table 5). The potential for cardiopulmonary resuscitation in these cases depended on how soon after the fatal event the body was discovered. Cardiopulmonary resuscitation was attempted in 10 cases.

In 38 cases (13%) it was not recorded whether the death had been witnessed. Of the remaining 139 people whose deaths were witnessed, cardiopulmonary resuscitation had been attempted in 48—in 22 by the person witnessing the death and in 26 by someone who had been called to the scene.

Ambulance crews were first to attempt cardiopulmonary resuscitation in 21 cases. In 20

Table 4 Number (and percentage) of deaths according to survival times from onset of symptoms and previous medical history of myocardial infarction

	0 min	*NK but < 10 min*	*NK but < 1 h*	*NK but < 24 h*	*NK but > 24 h*	*Not known*	*Total*
MI	14 (23)	12 (20)	9 (15)	20 (33)	6 (10)	11	72
no MI	38 (19)	44 (23)	23 (12)	72 (37)	18 (9)	29	224
Total	52	56	32	92	24	40	296

MI, myocardial infarction; NK, not known precisely.

Table 5 Type of person witnessing the death and attempting cardiopulmonary resuscitation

Witness	*Number of deaths*	*CPR attempts*
Spouse	47	4
Other family in household	25	6
Neighbour	15	6
Bystander	33	17
GP/deputy	4	1
Ambulance crew	4	21
Other	1	3
Person unknown	9	
No witness	119	
Not known whether witnessed	38	
Total	296	58

CPR, cardiopulmonary resuscitation; GP, general practitioner.

cases cardiopulmonary resuscitation could have been started earlier by the person who either witnessed or was first aware of the death, including two deaths at work. In a further three cases cardiopulmonary resuscitation was initiated by a general practitioner, an off-duty hospital doctor, and a district nurse.

Discussion

Although coronary mortality in Glasgow is high in international terms, there is no evidence to suggest an unusual pattern of coronary deaths, such as a high incidence of sudden cardiac death. The general pattern of coronary deaths outside hospital is typical and has not changed in 15 years (table 6).

Most coronary deaths occurred outside hospital and 85% of the victims were well in the 28 days before death. These data indicate that the potential for clinical measures to prevent coronary deaths outside hospital lies largely in the circumstances of the fatal event.

In Seattle and neighbouring King County, Washington, over 450 000 people have received basic instruction in the techniques of cardiopulmonary resuscitation, and it has been reported that the application of these techniques by lay persons, before the arrival of a mobile coronary care team, can increase long term survival rates from out of hospital cardiac arrest by 50%.[8]

In our study, 40% of the cardiac arrests outside hospital were unwitnessed. The earliest that cardiopulmonary resuscitation could have been attempted, therefore, was when the death was discovered. When the arrest was witnessed, about one quarter of individuals received cardiopulmonary resuscitation from a lay person before the arrival of medical help. To achieve similar results to those obtained in Seattle, it would be necessary to increase the number of people in the general public who are willing and able to carry out basic techniques in cardiopulmonary resuscitation.

Table 6 Comparison of fatal cases in Glasgow MONICA 1984 with Tower Hamlets 1970–3

	Glasgow MONICA (n = 420) (%)	*Tower Hamlets (1 10 11) (n = 350) (%)*
Place of death:		
Work	3	7
Home	51	47
Hospital	29	32
Other	17	14
Dead on arrival at hospital	21	34
Witnessed deaths outside hospital:		
Yes	47	53
No	40	43
Not known	13	5

Most deaths from coronary heart disease in Glasgow as in a previous study in Belfast[9] occurred at home. In deaths that were witnessed by the spouse or another member of the immediate family, cardiopulmonary resuscitation was attempted in only 14% of cases. Few people died at work, and six out of 13 bystanders in these cases attempted cardiopulmonary resuscitation. Bystanders also initiated cardiopulmonary resuscitation in about a half of witnessed deaths (nine out of 20) that occurred in a public place.

Most (57%) of the 87 cases where cardiopulmonary resuscitation could have been attempted, but was not attempted by the person witnessing or discovering the death occurred at home or at another private address in the presence of the spouse or other close relative. Campaigns to educate lay people in the techniques of cardiopulmonary resuscitation, whatever their impact on people in workplace settings or public places, will be of benefit in few cases, unless they lead to resuscitation being attempted by spouses and close relatives at private addresses.

A more selective approach would be to provide instruction in cardiopulmonary resuscitation for the relatives of patients who have survived a myocardial infarction. However, only 15 of the 72 people in the present study with a previous history of myocardial infarction died in the presence of their spouse or another member of the family household. Three of them received cardiopulmonary resuscitation before the arrival of medical help. The maximum impact of a family-based strategy would have been to provide cardiopulmonary resuscitation in 12 cases (4% of all deaths occurring outside hospital).

Because very few deaths (a maximum of 16 but probably nearer eight) occurred in the presence of ambulance crews or general practitioners, the potential benefit that might have been gained just by equipping emergency ambulances and general practitioners with defibrillators would be small in relation to the total number of deaths, however cost-effective these resuscitations may be in themselves.

The data not only show that medical help arrived almost always too late to have any prospect of reversing cardiac arrest, but also that measures to improve response times of general practitioners and ambulance crews are unlikely by themselves to improve the prognosis of people who have an out of hospital cardiac arrest. In 91% of the cases in this study the fatal collapse had occurred before the call for medical help was made.

For professional interventions to have more chance of success, it would be necessary either for cardiopulmonary resuscitation techniques to be underway when medical help arrives, or for the call for medical help to be made before the fatal collapse occurs.

It is not possible to tell from these data to what extent the fatal collapse was preceded by a prodromal period during which it may have been possible to make an earlier call for help. However, previous studies in which witnesses of sudden deaths were interviewed found that prodromal symptoms seldom bring patients under medical care more quickly.[10 11] A previous study of survivors of myocardial infarction in Glasgow showed a median delay of 4·1 hours in calling for help after the onset of symptoms.[12] This may not be typical of fatal cases.

We have considered the possibility that these data, which are based on registered deaths, do not take sufficient account of people who survived a cardiac arrest outside hospital, perhaps by provision of cardiopulmonary resuscitation or by prompt defibrillation, and who were then admitted to hospital. Such cases have been registered by the MONICA Project in subsequent years. Six people survived out of hospital cardiac arrest in 1985, and two in 1986 (Morrison C, personal communication). In four cases, cardiac output was reported as having been restored by bystanders, applying cardiopulmonary resuscitation before an ambulance or other medical help arrived. These findings suggest that successful cardiopulmonary resuscitation after a cardiac arrest outside hospital in Glasgow was a rare event in 1984.

There are of course other components of acute medical care for the cardiac arrest such as the relief of pain, treatment of ventricular failure, administration of thrombolytic therapy, and prompt delivery to a coronary care unit.[13] However, the main contribution of these measures to reducing mortality from coronary heart disease is likely to be an improvement in the prognosis of patients who survive to receive medical attention, most of whom already survive to reach hospital. About one third of all deaths from coronary heart disease belong in this category.

The data are based on events in 1984 when the ambulance service in Glasgow was not equipped to provide resuscitation for cases of cardiac arrest and only responded to direct calls from the general public when somebody had collapsed. They provide a baseline, therefore, against which the effect of developments in care can be assessed. Subsequently, ambulances have been equipped with defibrillators and crews have received training in their use and in cardiopulmonary resuscitation. After reorganisation of the Glasgow ambulance service in 1986, response times to emergency calls have been substantially improved, with 36% of cases being attended within seven minutes and 92% witin 14 minutes (Scottish Ambulance Service Statistics, ORCON Standard Times October/December, 1989). After a report from the National Audit Office in June 1991, the Scottish Office has indicated that additional funding may be made available to the Scottish Ambulance Service to further improve the response time to emergencies in the Glasgow area. We intend to repeat this study to assess the impact of these changes on the outcome of sudden deaths from coronary heart disease in Glasgow.

We are not aware of a previous analysis which assesses the potential impact of community coronary care schemes on the total number of deaths from coronary heart disease outside hospital. In Glasgow in 1984, there were few cases in which the provision of a defibrillator and extended training of ambulance crews could have made a difference to the fatal outcome. The greatest potential for saving lives seems to lie with the relatives of people in middle age in dealing promptly with acute coronary symptoms, calling for help early, and initiating cardiopulmonary resuscitation, so that these techniques are underway when professional help arrives. Should it prove possible to change behaviour in this area, then the provision of ambulances with defibrillators would have a much greater impact. Without it the number of successes may appear important when summated across the country, or compared with other life-saving services, but they are small both in relation to the total numbers of out of hospital deaths, and the expectations of many who are involved.

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1 Tunstall-Pedoe H. Uses of coronary heart attack registers. *BMJ* 1978;40:510–5.
2 Fulton M, Julian DG, Oliver MF. Sudden death and myocardial infarction. *Circulation* 1969;39 and 40(suppl IV):182–93.
3 Committee of Public Accounts, House of Commons. *Coronary heart disease, 26th report*. London: HMSO, 1989.
4 The principal investigators of the MONICA Project. WHO MONICA Project: geographic variation in mortality from cardiovascular disease. *World Health Stat Q* 1987;40: 171–84.
5 WHO MONICA Project Principal Investigators (Prepared by H Tunstall-Pedoe). The World Health Organisation MONICA Project (Monitoring Trends and Determinants in Cardiovascular Disease): a major international collaboration. *J Clin Epidemiol* 1988;41:105–14.
6 MONICA MANUAL. 2nd ed. Geneva: Cardiovascular Disease Unit, World Health Organisation, 1990.
7 McIlwaine WJ, Donnelly MDI, Chivers AT, Evans AE, Elwood JH. Certification of death from ischaemic heart disease in Belfast. *Int J Epidemiol* 1985;14:Pb560–5.
8 Cummins RO, Eisenberg MS. Cardiopulmonary resuscitation—American style. *BMJ* 1985;291:1401–3.
9 McIlwaine WJ, Donnelly MDI, Mallaghan M, *et al.* Deaths from ischaemic heart disease in Belfast. *Br Heart J* 1986;55:330–5.
10 Tunstall-Pedoe H, Clayton D, Morris JN, Bridgen W, McDonald L. Coronary heart attacks in East London. *Lancet* 1975;ii:833–8.
11 Tunstall-Pedoe H. A coronary heart attack register in East London. University of Cambridge, 1977, MD. University Microfilms Int 78–70,028.
12 Dunn G, Elms S, Melville DI, Lawrie TDV, Murray TS. Early treatment of myocardial infarction in the community: *BMJ* 1978;ii:1143–5.
13 Mathewson ZM, McCloskey BG, Evans AE, Russell CJ, Wilson C. Mobile coronary care and community mortality from myocardial infarction. *Lancet* 1985;i:441–3.

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PRACTICE REVIEWED

Management of myocardial infarction: implications for current policy derived from the Nottingham Heart Attack Register

J M Rowley, P Mounser, E A Harrison, A M Skene, J R Hampton

Abstract

***Objective*—A register of patients with heart attacks in the Nottingham Health District has been maintained since 1973. Data from 1982 to 1984 inclusive, a period before trials of thrombolytic therapy started in Nottingham, were analysed to provide background information for the introduction of a policy of routine thrombolysis for appropriate patients.**

***Design*—Data were collected prospectively on all patients transported to hospital in the Nottingham Health District with suspected myocardial infarction in the years 1982–84 and on patients treated at home during that time.**

***Setting*—Two district general hospitals responsible for all emergency admissions in the health district.**

***Patients*—6712 patients admitted to hospital with suspected myocardial infarction and 1887 patients found dead on arrival at hospital. Approximately 1500 patients in whom a myocardial infarction was suspected were treated at home, but only 125 were identified who had a definite or probable infarction.**

***Results*—Among the patients admitted within 24 hours of the onset of symptoms, the median delay from onset to hospital admission was 174 minutes; 25% of patients were admitted within 91 minutes. The only factor that seemed to affect the time taken was the patient's decision to call a general practitioner or an emergency ambulance. If a general practitioner referred the patient to hospital the median delay was 247 minutes, compared with 100 minutes when the patient summoned an ambulance. Ninety three per cent of all patients were transported by ambulance. The median time from the call for the ambulance to hospital arrival was 29 minutes. Once a patient was admitted to hospital, the time to admission and general practitioner involvement seemed relatively unimportant as predictors of outcome. Patients admitted more than nine hours after onset of symptoms with a diagnosis of definite or probable infarction had a poorer outcome than those admitted earlier (in-hospital mortality 22·4% *v* 13·1%). The fatality rates of those admitted to a coronary care unit or to an ordinary medical ward are similar.**

***Conclusion*—Although the introduction of thrombolytic therapy has brought with it an increased awareness of the need to minimise any delay in time to admission, it seems that in a predominantly urban area like Nottingham, patients with a suspected heart attack will continue to be admitted to hospital most quickly if an ambulance crew rather than a general practitioner is called. Because the ambulance crew was in contact with such patients for only a short time it seems unlikely that administration of a thrombolytic drug in the ambulance would be helpful.**

Disease registers have many functions. They can be used simply to describe disease prevalence and natural history, though clearly they can only record patients who die or who present to one of the medical services. They can be used to record patients with conditions such as diabetes or thyroid disease and timely medical assessment can prevent complications. Registers can also be particularly valuable for monitoring trends in the behaviour of patients with the disease and in providing the background information necessary for the rational introduction of new forms of treatment.

The early registers of patients with ischaemic heart disease[1 2] established the pattern of early death after the onset of symptoms in patients with heart attacks, and these observations paved the way for special ambulance facilities. The international registers supported by the World Health Organisation,[3] aimed mainly to give descriptive information to help plan provision of services for what was then seen as an "epidemic" of ischaemic heart disease. The Nottingham Heart Attack Register was set up in a simple form in 1973 and in a more definitive way in 1982 to monitor the introduction of new forms of ambulance service for patients with heart attacks, and at the same time to provide longitudinal information that might help to explain the changes in national mortality

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from ischaemic heart disease that were then expected.

The acceptance of the value of thrombolysis in patients with myocardial infarction,[4 5] and the recommendation that therapy is started as soon as possible after onset of symptoms has led to a need for a detailed description of the events that determine the way such patients are managed. The Nottingham register includes details of patient actions after the onset of symptoms and records the response of the medical services to requests for assistance. These data suggest guidelines for patient management which should enable appropriate patients to be given thrombolytic treatment as quickly as possible. We describe here an analysis of data collected during 1982–84 inclusive, when the value of defibrillation in cardiac arrest was established but that of thrombolysis was not.

Methods

Throughout 1982–84 the register was maintained by a non-medical graduate (Higher Clerical Officer Grade) supported by two clerical officers. Patient case records were reviewed by a physician (JMR) for diagnostic coding. Data were stored and analysed initially on the Nottingham University main computer. Subsequent analysis was carried out by the British Heart Foundation Cardiovascular Statistics Group.

EVENTS

The register documents events suggestive of myocardial infarction which occur in or near the Nottingham Health District (population approximately 600 000). Events are identified in several ways.

(i) Hospital admissions

Nottingham is served by two hospitals, University Hospital and City Hospital, but only University Hospital has an accident and emergency department. All patients transported by ambulance as a result of a patient-initiated emergency (999) call are taken there. Patients sent in as a result of general practitioner calls may be admitted to either hospital, depending on the emergency take-in rota. Those patients with an illness that might possibly have been a myocardial infarction are identified in the records of both the accident and emergency department at University Hospital and from the admissions records of the medical wards at both hospitals. In addition, the records of the Nottingham Ambulance Service, which has a single control centre, are inspected daily. This source is valuable in identifying appropriate cases for the register. All patients with a convincing clinical history are followed until death or hospital discharge.

(ii) Coroner's records

Coroner's records are reviewed for all patients found dead on arrival at hospital.

(iii) Patients treated at home

Between 1982 and 1984 a special district nurse service was offered to all general practitioners in the Nottingham Health District. Any general practitioner who wished to treat a patient with a suspected myocardial infarction at home was invited to request three visits on successive days from a district nurse who would record an electrocardiogram and take blood for the estimation of cardiac enzymes. The electrocardiograms were taken to University Hospital and reported immediately (JMR).

To obtain information on patients kept at home, but for whom the district nurse service was not used, the records of the biochemistry laboratories of the two Nottingham hospitals were monitored for general practitioner requests for the estimation of cardiac enzymes. In addition, domiciliary visit claim forms submitted by consultants who had been asked to record an electrocardiogram in a patient's home were collected for the single year 1984.

SCOPE OF ANALYSIS

Much of the data which define the time sequence of events from onset of symptoms to hospital admission—time of onset of symptoms, to whom first call for help was made, time to arrival of general practitioner, etc—was obtained via a patient inverview conducted shortly after admission. Most patients were interviewed, but administrative constraints or the patient's condition sometimes made an interview impossible. Those patients who were interviewed were effectively selected at random, with the obvious exception that patients who died soon after admission were more likely to be missed.

Timing data were much less complete for those cases who were certified dead on arrival or who died in the accident and emergency department. Here the most comprehensive data were obtained when the event involved a sudden collapse that was witnessed and provoked an immediate request for the emergency services. Such patients reach hospital soon after the onset of symptoms. However, they are not currently candidates for thrombolysis and their inclusion in an analysis of times to admission would lead to an inappropriate bias towards shorter time intervals. Our analysis, therefore, is restricted to those patients who were alive on arrival at hospital and who were admitted to a ward or coronary care unit.

Approximately 20% of all admissions in the register arrived at hospital more than 24 hours after onset of symptoms with many of these patients reporting an interval of three days or more. Most of these admissions were the result of complications evolving after the initial symptoms. Most of these patients contacted their general practitioner at some point before admission. However, the time at which the general practitioner became involved is more often given as a date, and precise times in this group are rare. These cases are included in the overall analysis which investigates patient decision-making and hospital outcome, but they are not included in the analysis of response times.

Although the 24 hour cut off is somewhat arbitrary, it is argued that we obtain a fairer picture of the relative contributions of patient picture of the relative contributions of patient action, general practitioner involvement, and the ambulance service to the overall time to admission in that group of patients who are believed to have the greatest potential to benefit from thrombolysis.

DEFINITIONS

Patients were assigned to diagnostic categories as follows:

"Definite" infarction—A convincing clinical history plus changes in the electrocardiogram diagnostic of recent infarction and raised concentrations of serum aspartate aminotransferase and serum hydroxybutyrate dehydrogenase to more than twice the upper limit of normal.

"Probable" infarction—A convincing clinical history plus either changes in the electrocardiogram suggestive of recent infarction or changes in the electrocardiogram not typical of recent infarction but associated with enzyme concentrations raised to more than twice the upper limit of normal.

"Possible" infarction—A convincing history plus either abnormalities in the electrocardiogram not typical of recent infarction or enzyme concentrations above the upper limit of normal.

Ischaemic heart disease—A convincing history plus electrocardiographic evidence of old infarction only.

The term "suspected infarction, not proven" was used to describe patients who were admitted because a myocardial infarction was suspected but examination showed a normal electrocardiogram and normal enzyme concentrations.

STATISTICAL ANALYSIS

Times between key events, onset of symptoms, call for general practitioner etc, were recorded in the database in two ways. Where possible, precise time intervals were calculated, but often the information was volunteered in the form of an estimate, for example, "a delay of between two and four hours". Medians and other quantiles were therefore calculated by linear interpolation on grouped data, Armitrage and Berry.[6] Because samples were large, there was very little loss of precision with this approach. All statistical tests comparing time distributions were carried out on similarly grouped data, using "location shift" models within the class of generalised logistic regression models described by McCullagh.[7]

Results

PATIENTS ADMITTED TO HOSPITAL

The register documents 8599 events during the 1982–84 period where a suspected myocardial infarction led to a request for hospital services. In 1887 cases, the patients were either certified dead on arrival or died in the accident and emergency department. Of these, 1497 (79·3%) were certified as having died of coronary heart disease. The other 6712 events resulted in admission to a ward or coronary care unit. Five thousand, eight hundred and seventy four (87·5%) of these events affected patients who lived within the district health authority boundary. Most of the remainder represented cross boundary flow from adjacent authorities.

TIME BETWEEN ONSET OF SYMPTOMS AND HOSPITAL ADMISSION

The time of both onset of symptoms and arrival in hospital is known for 4526 (67·4%) of the 6712 patients who survived to admission. In a further 1814 (27%), the interval between onset of symptoms and hospital arrival was given as a range—eg, 6–12 hours. Times to admission ranged from a few minutes to several days. Some 1350 patients were admitted more than 24 hours after onset of symptoms, this includes 903 admitted after an interval of more than 72 hours.

For those who were admitted within 24 hours the median time from the onset of symptoms to arrival in hospital was 174 minutes. Twenty five per cent arrived within 91 minutes and 75% by 353 minutes with 90% of these admissions presenting within 11·7 hours (fig 1). Time to admission was shorter for men than women (medians 167 and 202 minutes, $p < 0{\cdot}00001$), but was longer for patients eventually shown to have a definite or probable infarction compared with other diagnostic categories (medians 179 and 172 minutes, $p < 0{\cdot}05$). Patients aged 65 or less were admitted a little quicker than those aged over 65 years (medians 169 and 183 minutes, $p < 0{\cdot}05$). The differences between median times are small compared with the spread of values in each group.

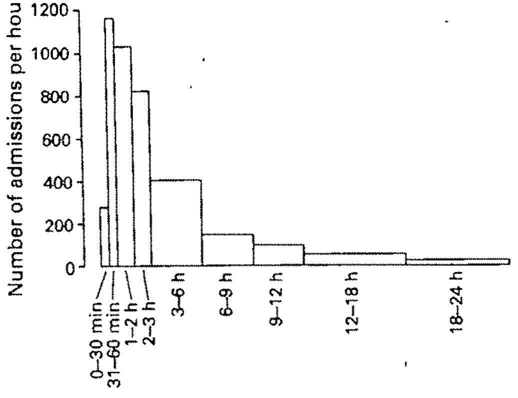

Figure 1 Distribution of time between the onset of symptoms and hospital admission in the patients admitted within 24 hours.

GENERAL PRACITIONER INVOLVEMENT

The most striking finding from the analysis of admission times was a considerable difference in time to admission between the group who called a general practitioner or deputising service and who were subsequently referred to hospital by this means (group A); and the group who did not call a general practitioner and whose admission was arranged by some other person (self, relative, work-mate, etc), usually by dialling 999 for an emergency ambulance (group B). In 5945 cases it was known whether an attempt had been made to contact a general practitioner. Four thousand and eighty four patients were known to have made some attempt and in 3841 of these cases the general

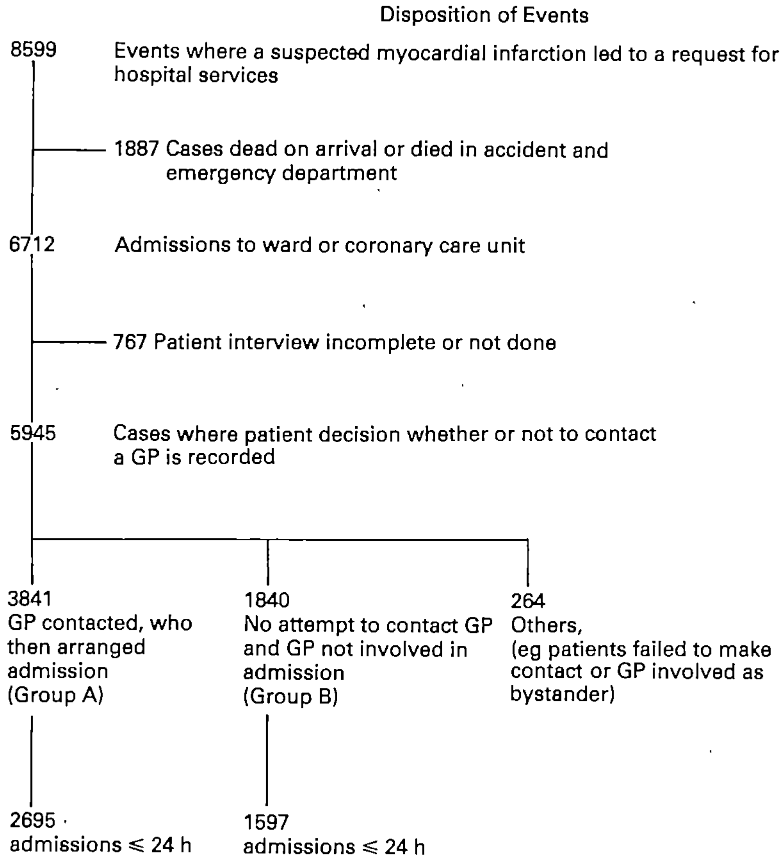
Disposition of Events
8599
Events where a suspected myocardial infarction led to a request for hospital services
1887 Cases dead on arrival or died in accident and emergency department
6712
Admissions to ward or coronary care unit
767 Patient interview incomplete or not done
5945
Cases where patient decision whether or not to contact a GP is recorded
3841
GP contacted, who then arranged admission (Group A)
1840
No attempt to contact GP and GP not involved in admission (Group B)
264
Others, (eg patients failed to make contact or GP involved as bystander)
2695
admissions ≤ 24 h
1597
admissions ≤ 24 h

Figure 2 Data available for analysis of patients' decision whether or not to contact a general practitioner.

practitioner then arranged the admission (group A). The difference represents patients who either failed to make contact or who then arranged their own admission. It is known that in 1861 events the patients did not attempt to contact a general practitioner and that 1840 of these were admitted to hospital without any subsequent general practitioner involvement (group B), the difference is due to those events where a general practitioner was involved as a bystander (fig 2).

Two thousand, six hundred and ninety five (70%) of all group A admissions occurred within 24 hours compared with 1597 (87%) of the group B admissions. For those admitted within 24 hours, the median delay was 247 minutes in group A, but only 100 minutes in group B ($p < 0{\cdot}0001$). The decision by the patient, his relatives, or bystanders to call a general practitioner or an emergency ambulance greatly influenced the delay before hospital admission.

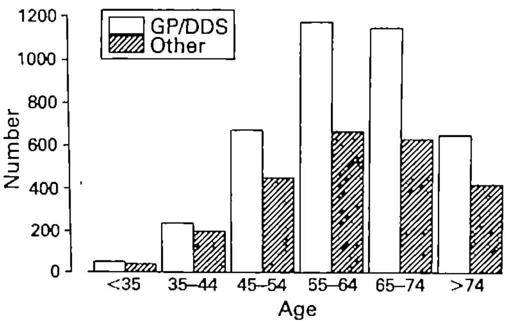

Figure 3 Classification of admissions by age and involvement of a general practitioner, the doctors' deputising service, or other means of hospital admission (usually by direct call for an emergency ambulance).

Figure 3 shows admissions by age decades and route of referral. A general practitioner was more likely to be involved if the patient was in the 55–75 year age range. However, it is not possible to determine directly whether this is because older patients were more likely to call a general practitioner or because general practitioners are effective in identifying patients in the younger age range who do not require hospital admission.

Among patients admitted within 24 hours, the delay in hospital admission associated with the involvement of the general practitioner seems to be due, in part, to the patient's action. Direct calls for an ambulance by a patient were made sooner after the onset of symptoms than calls for help to a general practitioner. The median interval from onset of symptoms to a call for an ambulance was estimated to be 74 minutes for those patients in group B admitted within 24 hours. The corresponding estimate calculated from group A patients admitted within 24 hours for the interval from onset of symptoms to calling a general practitioner is 106 minutes. However, for these same patients the estimated median interval from the onset of symptoms to the eventual call for an ambulance was 206 minutes, the difference reflecting the time taken for the general practitioner to visit the patient and decide on a course of action.

ROLE OF THE AMBULANCE SERVICE

The mode of transport to hospital was recorded in 6056 (90%) of the 6712 admissions. Most of these (5586 (92%)) patients were carried by ambulance. Similar proportions of patients eventually shown to have had a definite or probable infarction or other diagnoses were carried by ambulance (93% and 92% respectively). Transport other than by ambulance was more likely to be used when symptoms began away from home: 17% of such patients did not call for an ambulance, but when the symptoms began at home only 6% of patients used other transport.

Details of the times taken for the ambulance to reach patients and transport them to hospital were known in 4988 patients (89% of those carried by ambulance). The median time taken by the ambulance to reach the patient after receipt of the call was seven minutes. The interquartile range for these data was 5–11 minutes—ie, 50% of all times lay within this interval. The median time to arrival was essentially the same for men and women, for those aged 65 or less and those aged over 65, and for those eventually found to have had a definite or probable myocardial infarction and those in other diagnostic categories. It is not possible to determine the effect of the general practitioner on the time to arrival of an ambulance because general practitioners can summon an ambulance either by using a 999 call or by placing a routine request, but timing data are not complete in many of the cases of a routine request.

The median interval from the call for an ambulance to the arrival of the patient in hospital was 29 minutes (interquartile range 23–39 minutes). Therefore, the ambulance

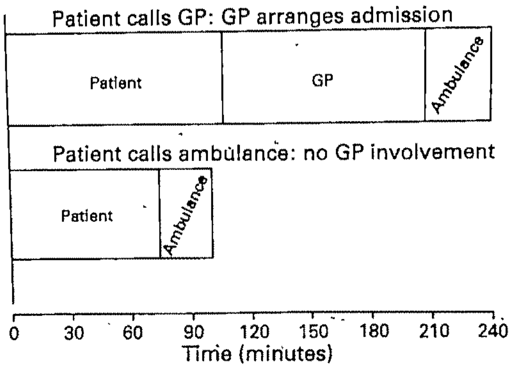

Figure 4 Median delays attributable to patient, general practitioner, and ambulance.

crew was actually in contact with the patient for about 22 minutes. Part of that time was taken loading the patient into the ambulance and part by the journey to hospital.

The median times from the call for the ambulance to arrival of the patient in hospital were within one minute for men and women, for those aged 65 or less or 65 and over, and for those eventually shown to have had a definite or probable infarction and those in other diagnostic categories. There was, however, a significant difference between the groups of patients who did or did not involve a general practitioner. The median interval from the call to the ambulance to hospital admission was 32 minutes (interquartile range 25–43 minutes) when the patient called a general practitioner and 26 minutes (interquartile range 21–31 minutes) when he did not ($p < 0.0001$). Figure 4 summarises the various components of the overall delay between onset of symptoms and hospital admission and emphasises the additional delay that results from general practitioner involvement.

FACTORS AFFECTING THE PATIENT'S DECISION TO INVOLVE A GENERAL PRACTITIONER

(a) Place where symptoms began

As might be expected, the place where the patient was taken ill played a major role in his or her decision to call a general practitioner. The place where symptoms began is known for 6338 (94%) of all admissions. For these patients, 80% were at home when symptoms started, 5% started, 5% were at work, and 15% were at other places away from home. 74·8% of those at home, 38·2% of those at work, and 40·4% of those at other places called their general practitioner.

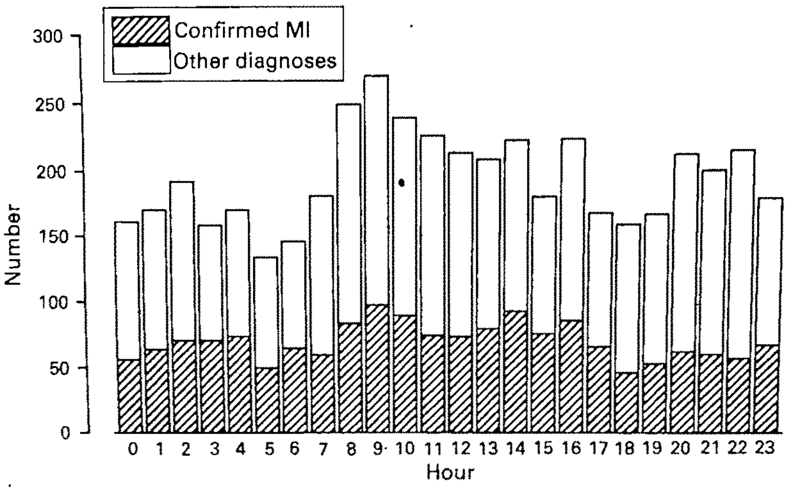

Figure 5 Classification of admissions by hour of onset of symptoms and eventual diagnosis.

If the symptoms began at home the call for help was made from home in 95% of cases. In the remainder, patients seem to have continued with their planned activities and then subsequently called from work, relatives, etc.

(b) Time of onset of symptoms

Among patients who could give a reasonably precise time of onset of symptoms the distribution of hour of onset showed a peak between 8 and 10 am. The data were not consistent with the hypothesis that major symptoms are equally likely to develop at any time of day ($p < 0.01$). A similar pattern was observed both for all patients with suspected myocardial infarction and for those eventually shown to have a definite or probable infarction (fig 5) but there was also evidence that these patterns were not identical. The second peak seen in the evening was not found in the group with a definite infarct. Symptoms that develop in the mid-evening were less likely to be associated with a diagnosis of definite or probable infarction.

The decision to call a general practitioner was not directly associated with time of day, but because more people were away from home during the day the percentage calling a general practitioner varied from 57% when symptoms started in the early afternoon to 74% during the early hours of the morning. The time from onset of symptoms to admission was also associated with time of onset. A two-way analysis of variance applied to the log times suggests that the mean time to admission tended to be a little longer when symptoms started during the early hours of the morning but was relatively constant over the rest of the day. The effect of contacting a general practitioner increased the *mean* time to admission by a factor between 2·5 and 3, but this multiplier was constant over the day.

DIAGNOSIS AND OUTCOME

Diagnosis and involvement of general practitioner

Table 1 shows the confirmed in-hospital diagnosis for those patients whose admission was arranged by a general practitioner and contrasts this with all other admissions. Overall there was a slight but significantly greater percentage of admissions with a definite or probable myocardial infarction in the patients referred by a general practitioner (35·1% *v* 30·4%, $p < 0.0001$). However, as table 2 indicates, the accuracy of the general practitioner in identifying patients with myocardial infarction exceeds self selection only in the over 65 age group. The accuracy of general practitioners in the initial diagnosis may be due in part to the nature of the illness in the patients who choose to contact them. It was noted above that such patients are known to wait longer before calling for help than those who are admitted without contacting a general practitioner, suggesting differences in symptom pattern or severity between the two groups.

Table 1 Admission route and confirmed diagnosis (%)

Diagnosis	*Admission arranged by general practitioner or deputising service (n = 3929)*	*Other admissions (n = 2390)*
Definite MI	17·4	18·9
Probable MI	17·7	11·5
Possible MI	43·1	44·4
IHD	3·7	4·8
SINP	14·1	16·8
Other diagnosis	3·9	3·6

MI, myocardial infarction; IHD, ischaemic heart disease; SINP, suspected infarct not proven.

Table 2 Percentage of patients with definite or probable myocardial infarction by route of referral and age

Age	*General practitioner or deputising service*	*Self*
<45	21·5	22·8
45–54	31·6	33·4
55–64	37·5	36·6
65–74	39·4	30·8
>74	33·1	21·3

ADMISSION TO CORONARY CARE UNIT OR MEDICAL WARD

Although there were 13 coronary care unit beds available at the two hospitals, only 64·5% of all admissions were admitted direct to the coronary care units. Thirty eight percent of all patients admitted to a coronary care unit were eventually diagnosed as having a definite or probable myocardial infarction. Table 3 shows the proportion of patients admitted to a coronary care unit by age, sex, and eventual diagnosis. It shows that older patients were less likely to be admitted to a coronary care unit. Among the elderly, men were more likely to be admitted to the coronary care unit than women. This difference is apparent both in the group of patients who have a definite or probable myocardial infarction and in the group who go on to have other confirmed diagnoses.

Outcome

The case fatality rate in hospital for all admissions with suspected myocardial infarction was 931 of 6712 (13·9%). For patients with a diagnosis of definite or probable myocardial infarction the rate was 17%, compared with 12·3% for other diagnoses. Mortality in the possible myocardial infarction group was 14·2% and in the group in whom a suspected infarct was not confirmed it was 8·5%. Such rates were not unexpected, given the definitions for each diagnostic class. Most deaths in the groups with possible myocardial infarction and suspected infarct not proven were attributed to cardiac causes. However, electrocardiographic or enzyme evidence confirming infarction had not been obtained before death.

Information about survival, age, and referral to hospital was known for 6267 patients. As would be expected, fatality rates increased considerably with increasing age. There is no evidence, however, that route to hospital had an effect on case fatality for any age group.

The fatality rate for patients admitted to a coronary care unit was lower than for those admitted to a ward (11·0% compared with 18·7%) but the difference is mainly due to the different age structure of these groups. Table 4 shows mortality by age decades and coronary care unit/ward admission. Ward and coronary care unit fatality rates were almost identical through most of the age range but there was an increased mortality in the coronary care unit for patients over 75 years of age.

Effect of delay in hospital admission on outcome

It was difficult to assess the effect of time from onset of symptoms to hospital arrival on the eventual fatality rate in hospital as times were not available for many of the patients who died soon after admission. Hospital outcome could be related to the duration of symptoms before admission in 6318 patients, among whom the fatality rate in hospital was 12·7%. In contrast, the hospital fatality rate was 33·5% in the group of 379 patients for whom insufficient information was available.

Table 5 gives in-hospital mortality by time to admission for those patients who were able to provide the timing data. Delay in admission had very little effect except that there was a higher fatality rate among patients with a definite or probable infarct who were admitted late. For those with a pre-hospital illness lasting nine hours or less, the fatality rate in hospital was 13·1%, while for those with symptoms for more than nine hours it was 22·4%.

PATIENTS TREATED AT HOME

The domiciliary diagnostic service was offered to all 315 general practitioners in the Nottingham District Health Authority. In the three years 1982–84 inclusive, 97 general practitioners used it: 60 used it for five patients or fewer, seven for between six and 10 patients, and 30 for more than 10 patients.

The district nurses visited 381 patients to record an electrocardiogram and take blood samples for the estimation of cardiac enzymes. Definite or probable infarction was diagnosed in 62 patients (16·3%). Possible infarction was diagnosed in 179 (47·0%), ischaemic heart disease in 10 (2·6%), and suspected infarct not proven in 130 (34·1%).

In addition to these patients, a search of the records of the biochemistry departments showed that during these three years, blood samples from 968 patients had been sent by general practitioners for the estimation of cardiac enzymes. Although the age and sex were not always known, these patients were apparently somewhat younger than those seen by the district nurses. In 63 patients one or more enzymes were increased to twice the

Table 3 Percentage of patients admitted to coronary care unit by sex, age, and diagnosis

	Definite/probable myocardial infarction		*Other diagnosis*	
Age	*Male*	*Female*	*Male*	*Female*
<55	93·6	85·2	82·8	77·5
55–64	89·0	89·2	77·9	72·9
65–74	71·3	50·3	56·2	39·9
>74	28·6	18·3	24·1	11·7

Table 4 Percentage in-hospital fatality in each age group of patients admitted to coronary care unit or medical ward

	Patients admitted to:	
Age	*Coronary care unit*	*Ward*
<55	3·9	3·8
55–64	9·4	9·3
65–74	19·1	19·2
>74	32·9	26·4

upper limit of normal, suggesting a diagnosis of probable infarction. In 342 patients, one or more enzymes were increased but to less than twice normal, making a diagnosis of possible infarction, and in 563 the cardiac enzymes were within the normal range.

During the single year 1984, 57 general practitioners in the Nottingham District Health Authority requested a domiciliary visit by a consultant physician to a patient suspected of having had a heart attack. No diagnostic information was available in these patients, but cardiac enzymes were not identified as having been requested in any of them. Eleven were admitted to hospital as an emergency as a result of the visit.

It is thus estimated that about 1500 patients with suspected myocardial infarction were treated at home by general practitioners during the three year period. Only 125 of these were known to have had a definite or probable infarction, however.

Discussion

The value of early specialised care for patients with heart attacks has been apparent since the development of the defibrillator. The demonstration that thrombolytic therapy is most beneficial when given soon after the onset of symptoms has provided another reason for rapid management decisions. The traditional role of the general practitioner as the patient's immediate source of help has to be reconsidered.

Our survey of patients with suspected myocardial infarction who were treated at home shows that this is a relatively uncommon practice even in our area, where the possibility of home care has been quite extensively investigated and discussed.[8] Our general practitioners made relatively little use of the diagnostic service provided by district nurses, and this was stopped at the end of 1984. Diversion of all the patients with definite or probable myocardial infarction from home to hospital care would have relatively little impact on the demand for hospital services, and from the end of 1984 we decided that there was little point in continuing to monitor patients treated at home. Clearly the main debate concerns the best way of arranging hospital admission.

Table 5 Percentage in-hospital fatality by time to admission

Time	*All admissions*	*Definite/probable myocardial infarction*
0–30 min	15·1	24·2
31–60 min	8·6	12·5
1–2 h	11·1	12·4
2–3 h	10·7	11·5
3–6 h	13·0	15·6
6–9 h	11·5	9·7
9–12 h	15·9	27·7
12–18 h	11·2	20·0
18–24 h	20·5	28·9
>24 h	15·7	20·6

We have shown that the median delay from onset of symptoms to hospital admission in the years 1982–84 was nearly three hours, and that there was little difference between subgroups of patients in terms of age, sex, or eventual diagnosis. The only fact that materially seemed to affect delay in admission was the patient's initial decision to call for an emergency ambulance direct or to seek help in the first instance from his general practitioner.

Given the size of the additional delay attributed to general practitioner involvement, the question arises whether this is biased in any way by the manner in which the data has been collected. It is accepted that most of the intervals were obtained via patient interviews and that such interviews miss patients who die in the first few days after admission. Table 5 shows that in-hospital fatality rates are effectively unrelated to time to admission although the observed rates are higher among patients admitted within 30 minutes. This finding, though not statistically significant, is consistent with an observation derived from the ASSET study[5] database that patients admitted within one hour have an increased risk of dying within one day, compared with patients admitted from two to five hours after onset of symptoms. Timing data is therefore more likely to be missing for very rapid admissions and this bias will increase the measurement of the times to admission, the effect being more marked in the self admission group. Our estimate of the additional delay attributed to general practitioner involvement is probably conservative.

We showed that patients who call for an emergency ambulance do so more quickly than those who call a general practitioner but our data do not point to any reason for this difference. It is possible that more severe symptoms tend to make patients summon an ambulance, but the proportion of patients eventually found to have a definite or probable infarction was essentially the same whatever the route of the call. General practitioners only seemed to admit to hospital a higher proportion of patients with definite or probable infarction than did 999 calls in elderly patients: this may indicate a reluctance to risk making an inaccurate diagnosis in the young. Our data suggest that the involvement of the general practitioner has little effect on outcome, though we have not been able to assess the value of pain relieving drugs given by general practitioners nor do we have data on patients seen by general practitioners because of chest pain but in whom myocardial infarction was not suspected.

Some of these data were used by the British Heart Foundation Working Party,[9] which concluded that there is little point—at least in an urban area—for thrombolytic therapy to be given either by general practitioners or by ambulance crews. The median delay between the call for an ambulance and its arrival is only seven minutes, and the patient is in hospital 22 minutes later, so there is little to be gained from beginning treatment out of hospital. Thrombolytic agents can cause bradycardia and hypotension, and the danger of giving treatment immediately before an ambulance journey, coupled with the extra delays that such treatment involves, might well outweigh any benefit gained from earlier treatment. We accept, however, that the situation may be different in rural areas.

It is difficult to compare the different time intervals that contribute to the total period from onset of symptoms to hospital admission in our study with those of previous reports, because the data were collected in different ways, and in most studies there was no distinction made between calls made to a general practitioner or an emergency ambulance. However, a study of patients in Tower Hamlets found that 31% of patients had contacted their general practitioner within one hour of the onset of symptoms, and 46% by two hours; 45% of patients were in hospital within four hours.[10] In Teeside, the median interval between onset of symptoms and the call for a general practitioner was 71 minutes and a median of 74 further minutes elapsed before an ambulance was called.[11] In Doncaster, the median delay before the call for help was 110 minutes.[12] In Edinburgh, a median delay from onset of symptoms to hospital admission was 5 hours 23 minutes if a general practitioner was involved, but 2 hours 21 minutes for a group of 60 patients who called an emergency ambulance.[2] Though our register data suggest a long delay is associated with general practitioner calls, this is evidently not inevitable as it has been found that a rapid response is possible with careful organisation: in Grampian, 67% of 511 patients were reached by general practitioners within two hours of the onset of symptoms.[13]

Once the patient has arrived in hospital it is clearly immaterial whether he was admitted by a general practitioner or whether he summoned an emergency ambulance directly. Delay in hospital admission had no clear effect on in-hospital fatality, except that there was a higher fatality rate among patients whose admission was arranged after a very prolonged period and in whom complications had presumably already developed. It is, however, difficult to be certain about the effect of delay in calling for help, because when patients died soon after admission, data tended to be incomplete.

Despite the presence of seven and six coronary care unit beds respectively in the two hospitals, approximately one third of patients were admitted in the first instance to a medical ward. The similarity in fatality rates between groups of patients admitted to wards or coronary care units has been described previously,[14] but since we do not know how or why patients were selected for either form of management it would not be reasonable to infer that coronary care units provide little or no benefit.

Though it seems desirable to educate patients to call for help quickly and to call for an ambulance rather than a general practitioner, attempts to do so have had little success.[15] The greatest potential for reducing the delay in hospital admission lies in the 100 minutes that elapse between the call for a general practitioner and the call for the ambulance. General pracititioners should be prepared to make a diagnosis on the basis of information given to them by the patient on the telephone and unless they can reach the patient within 10 or 15 minutes they should send an ambulance. General practitioners, and the receiving staff in accident and emergency departments, will have to accept that the diagnosis will on occasion be wrong, and patients will have to accept that when a myocardial infarction is possible a visit by their general practitioner may not be appropriate.

The maintenance of a register of patients with suspected myocardial infarction has only been possible because of the enthusiastic co-operation of consultant and general practitioner colleagues, of district nurses and nurses in the coronary care unit, medical wards, and of the staff in the accident and emergency department at University Hospital; we gratefully acknowledge their help. The research aspects of this study were supported by a grant from the Department of Health and Social Security.

1 Kinlen LJ. Incidence and presentation of myocardial infarction in an English community. *Br Heart J* 1973;35:616–22.
2 Armstrong A, Duncan B, Oliver MF, Julian DG, Donald KW, Fulton M, *et al.* Natural history of acute coronary heart attacks. A community study. *Br Heart J* 1972;34:67–80.
3 World Health Organisation. *Myocardial infarction community registers.* Copenhagen: WHO, Regional Office for Europe, 1976.
4 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction: Isis-2. *Lancet* 1988;ii:349–60.
5 Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian study of early thrombolysis (ASSET). *Lancet* 1988;ii:525–30.
6 Armitage P, Berry G. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1987:31.
7 McCullagh P. Regression models for ordinal data (with discussion). *J Roy Statist Soc B* 1980;42:109–42.
8 Hill JD, Hampton JR, Mitchell JRA. A randomised trial of home-versus hospital management for patients with suspected myocardial infarction. *Lancet* 1978;i:837–41.
9 British Heart Foundation Working Group. Role of the general practitioner in managing patients with myocardial infarction: impact of thrombolytic treatment. *BMJ* 1989;299:555–7.
10 Tunstall-Pedoe H, Clayton D, Morris JN, Brigden W, McDonald L. Coronary heart attacks in East London. *Lancet* 1975;ii:833–8.
11 Colling A, Dellipiani AW, Donaldson RJ, MacCormack P. Teeside coronary survey: an epidemiological study of acute attacks of myocardial infarction. *BMJ* 1976;ii:1169–72.
12 Smyllie HC, Taylor MP, Cuninghame-Green RA. Acute myocardial infarction in Doncaster. II-Delays in admission and survival. *BMJ* 1972;i:34–6.
13 Pai GR, Haites NE, Rawles JM. One thousand heart attacks in Grampian: the place of cardiopulmonary resuscitation in general practice. *BMJ* 1987;294:352–4.
14 Hill JD, Holdstock G, Hampton JR. Comparison of mortality of patients with heart attacks admitted to a coronary care unit and an ordinary medical ward. *BMJ* 1977;ii:81–3.
15 Rowley JM, Hill JD, Hampton JR, Mitchell JRA. Early reporting of myocardial infarction: impact of an experiment in patient education. *BMJ* 1982;284:1741.

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TECHNOLOGY

The Inoue balloon for dilatation of the tricuspid valve: a modified over-the-wire approach

T R D Shaw

Abstract

The Inoue balloon was used for dilatation of tricuspid stenosis in a 74 year old woman. The valve was reached by an over-the-wire approach with a 0·025 exchange length guide wire. The Inoue stylet would not reach the tricuspid orifice because the right atrium was so large. The Inoue balloon's special dilatation characteristics allowed good positioning at the tricuspid orifice. After dilatation to 27·5 mm, the pressure drop across the valve was reduced from 12 to 5 mm Hg. Further dilatation at 30 mm, however, created moderately severe tricuspid reflux without a further reduction of gradient.

The Inoue balloon is suitable for dilatation of tricuspid stenosis but small increments in dilatation size may be required for optimal reduction in gradient without creating significant reflux.

There is still only limited experience of balloon dilatation for tricuspid stenosis but there have been reports of successful relief of tricuspid stenosis, rheumatic[1–4] and congenital[5] and of combined dilatation of the tricuspid and mitral valves[6 7] and even triple valve dilatation of tricuspid, mitral, and aortic stenosis.[8] Tricuspid bioprosthetic valves have also been improved by balloon dilatation.[9 10] In these cases, standard tubular polyethylene or polyvinyl balloons have been used, being passed to the tricuspid valve orifice over a guide wire advanced to the pulmonary artery or right ventricular cavity. In the patient reported here, it was decided to use the Inoue balloon, though it was designed for the mitral valve, because the patient had a giant right atrium and a very small right ventricle—features which would have made placement of a tubular balloon at the orifice much more difficult. The design of the Inoue balloon is unique. Its walls contain a network of synthetic nylon fibres which give different compliance characteristics to its distal, proximal, and middle segments, so that at inflation the distal portion of the balloon enlarges first, allowing this portion to be drawn back against the stenosed orifice. On further inflation, the proximal segment enlarges, holding the balloon at the vale orifice which is then dilated as the middle segment expands at full inflation. The short length of the Inoue balloon and its blunt distal point reduce the risk of perforating the myocardial wall. The deflated Inoue balloon does not have a low profile, and to allow passage through the skin (and though the atrial septum for dilatation of the mitral valve) a metal stretching tube is included in the balloon equipment set. This is inserted into the balloon catheter lumen and causes the deflated balloon to be stretched into a lower, more rigid shape. The Inoue balloon catheter has no intrinsic curve and when it is used to dilate the mitral valve a curved stylet wire is inserted to arc the balloon towards the mitral valve. When the Inoue balloon was used to dilate the tricuspid valve in this case, it was found possible to use it in a modified over-the-wire approach.

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Case report

The patient was a 74 year old women who had no history of rheumatic fever. However, mitral valve disease had been noted during her first pregnancy at age 22. When aged 61, she had a pacemaker implanted because of lightheadedness caused by episodes of sinus arrest. The surgeon was unable to pass the pacing electrode across the tricuspid valve and an epicardial pacing system was implanted. A diagnosis of mild mitral stenosis, mild mitral reflux, and moderate tricuspid stenosis was made at this time. When she was 67 the pacemaker ceased functioning but she was then in atrial fibrillation without excessively long RR intervals and the pacemaker was not renewed. Marked ascites was noted at age 70; this responded to diuretic treatment. By the age of 74 she had breathlessness at rest and was restricted to walking 50 yards. She now had chronic ascites despite taking frusemide 160 mg per day. Echocardiography showed she still had mild mitral stenosis (pressure half time 125 ms), mild mitral reflux, and severe tricuspid stenosis (pressure half time 300 ms: estimated valve area 0·7 cm^2). She had chronic anaemia due to diverticulitis and telangiectasia of the stomach. She had had a previous nephrectomy and had moderate renal impairment. She was referred to the Western General Hospital for balloon dilatation of the tricuspid valve.

On examination, she was a thin, frail woman (45 kg, height159 cm) in atrial fibrillation with a controlled ventricular rate. The jugular venous pressure was raised to beyond the ears and the liver was four finger breadths enlarged and slightly pulsatile. She had moderate ascites

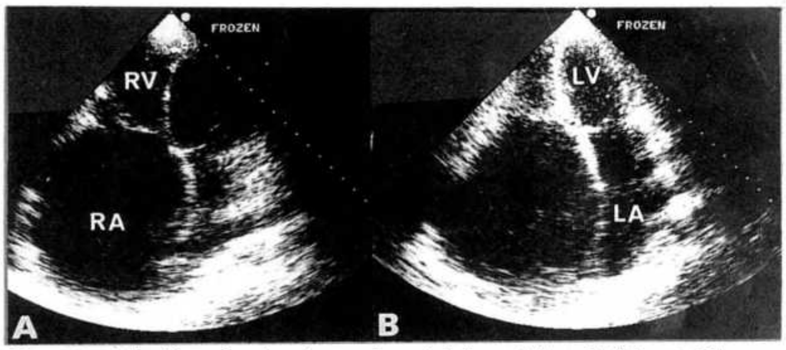

Figure 1 Apical four chamber views to show right heart (A) and left heart (B).

with slight sacral and ankle oedema. On auscultation a 3/6 tricuspid diastolic murmur and 1/6 mitral diastolic murmur were audible.

At echocardiography (fig 1) the mitral valve was only mildly stenosed with slight cusp thickening. Left ventricular function was normal. The right atrium was huge (9·7 × 10·8 cm in the apical view) and the atrial septum bulged into the left atrial cavity. The tricuspid valve cusps were thin but showed minimal opening.

At right heart catheterisation, the 3 cm curve Brockenbrough catheter and 0·035 exchange guide wire were negotiated with difficulty through the tricuspid valve. Right atrial pressure was 33/22 (mean 26) mm Hg and right ventricular pressure was 47/5–16 mm Hg. Cardiac output was 3·7 l/min and diastolic filling time 37 s/min with a mean tricuspid transvalvar gradient of 12 mm Hg, giving a valve area, calculated from the Gorlin formula ($3700 \div 44{\cdot}3 \times 37 \times \sqrt{12}$) of 0·65 cm². A right ventricular injection of contrast confirmed the absence of tricuspid reflux.

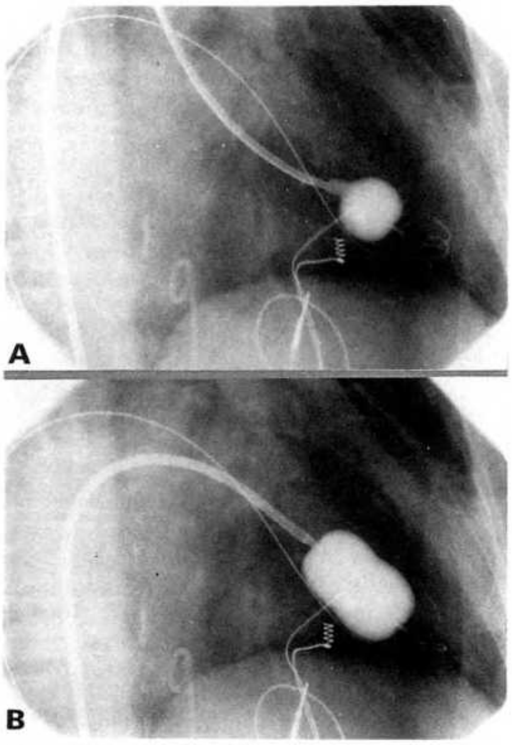

Figure 2 Inoue balloon dilatation at the tricuspid valve. (A) The distal portion of the balloon has been dilated. (B) The balloon catheter has been pulled back to engage the distal portion of the orifice and the balloon has been fully dilated. A 0·035 inch guide wire also lies across the tricuspid valve. An epicardial pacemaker system is in situ and an F6 pigtail catheter lies in the descending aorta to monitor systemic pressure.

The 0·035 inch exchange guide wire remained in the right ventricle, the Brockenbrough catheter was removed, and a Block double lumen catheter (USCI) was passed over the wire to the right ventricle. An exchange length 0·025 inch wire was then passed via the Block second lumen to lie alongside the 0·035 inch wire and the Block catheter was withdrawn. The Inoue balloon, with stretching metal tube inserted, was then passed percutaneously over the 0·025 inch wire to the right atrial cavity and the metal tube withdrawn. The 0·035 inch wire was retained within the right ventricle to maintain access across the tricuspid valve. The Inoue balloon was advanced over the 0·025 inch wire which took up a position around the superior border of the right atrium before descending to cross the tricupsid valve. The Inoue balloon followed over the wire and across the tricuspid orifice. The distal portion of the balloon was inflated and the Inoue catheter shaft was drawn back until the distal portion of the balloon was held against the tricuspid orifice. The balloon was then inflated to 27·5 mm (fig 2). On deflation, the Inoue balloon and 0·025 inch guide wire were ejected back into the right atrium. The Block double lumen catheter was re-advanced over the 0·035 inch wire to the right ventricle and its second lumen was used for pressure measurement simultaneously with right atrial pressure measurement via the Inoue balloon lumen. The tricuspid valve gradient had been reduced to 5 mm Hg with no increase in valve reflux. It was decided to attempt a greater reduction of gradient. With its stylet inserted, the Inoue balloon pointed towards the tricuspid valve but would not reach to the orifice. The 0·025 inch guide wire was therefore replaced into the right ventricle through the double lumen catheter and the Inoue balloon again followed over the wire to the tricuspid orifice.

The valve was dilated to 30 mm. A right ventricle angiogram now showed moderately severe tricuspid reflux: the valve gradient had incresed to 7 mm Hg, with right atrial pressure 32/18 mm Hg and right ventricular pressure 39/5–18 mm Hg. Cardiac output had risen slightly to 3·9 l/min: assuming tricuspid reflux at 33% of stroke volume, valve area increased to 1·56 cm².

The patient tolerated the procedure well and the next day she returned to the referring hospital and was discharged home a few days later. One month after the procedure her daughter reported that her breathlessness was much better and that the patient's general appearance and oedema were improved, with slight increase in exercise capacity. Doppler assessment showed that the tricuspid valve area had increased to 1·9 cm². At seven months and one year after valve dilatation, there continued to be evidence of moderately severe tricuspid reflux and mild stenosis. The patient's condition then gradually declined and she died in heart failure 13 months after the procedure.

Discussion

The Inoue balloon was used to dilate the tricuspid valve in this patient because of the considerable discrepancy between the atrial and ventricular sizes which would have made it difficult to obtain a stable orifice position with polyethylene balloons. Chen *et al* had previously used the Inoue balloon for combined dilatation of the tricuspid and pulmonary valves.[11] The Inoue balloon, with its metal stretching tube inserted could be advanced over a 0·025 inch guide wire: the stretching tube was essential for passing the balloon percutaneously to reach the right atrial cavity. Once the stretching tube was removed the Inoue balloon followed by an over-the-wire approach to the tricuspid orifice. The Inoue stylet was unable to direct the balloon to the orifice with such a giant right atrium. This over-the-wire approach might also be applicable in occasional cases of mitral stenosis where there is difficulty in crossing the mitral orifice.

Considerable reductions in valve gradient and an increase in valve area have been reported for rheumatic tricuspid stenosis[1-4 6-8] usually without development of tricuspid reflux. In the case report here, the final area was comparable to that obtained with double balloon dilatation but it was associated with the onset of significant tricuspid reflux. Bourdillon *et al* also found that reduction of stenosis was accompanied by the development of tricuspid incompetence: at subsequent tricuspid valve replacement, two of the three tricuspid commissures had been opened but no leaflet tear was found.[12] To avoid tricuspid reflux, small progressive increases in dilatation diameter, as is possible with the Inoue balloon, may be an advantage in obtaining the optimal balance between gradient reduction and development of valve incompetence. In this patient we expected that it might be difficult to position the balloon and only two dilatation diameters were used: in retrospect, small increases might have given a better haemodynamic result, although in this valve dilatation could be carried out only at a very advanced stage of valve disease.

1 Al-Zaibag M, Ribeiro P, Al-Kasab S. Percutaneous balloon valvotomy in tricuspid stenosis. *Br Heart J* 1987;57:51–3.

2 Khalilullah M, Tyagi S, Yadav BS, Jain P, Choudhry A, Lochan R. Double-balloon valvuloplasty of tricuspid stenosis. *Am Heart J* 1987;114:1232–3.

3 Ribeiro P, Al-Zaibag M, Al-Kasab S, *et al.* Percutaneous double balloon valvotomy for rheumatic tricuspid stenosis. *Am J Cardiol* 1988;61:660–2.

4 Goldenberg IF, Pedersen W, Olsen J, Madison JD, Mooney MR, Gobel FL. *Am Heart J* 1989;118:417–9.

5 Lokhandwala YY, Rajani RM, Dalvi BV, Kale PA. Successful balloon valvotomy in isolated congenital tricuspid stenosis. *Cardiovasc Intervent Radiol* 1990;13:354–6.

6 Bethencourt A, Medina A, Hermandez E, *et al.* Combined percutaneous balloon valvuloplasty of mitral and tricuspid valves. *Am Heart J* 1990;119:416–8.

7 Berland J, Rocha P, Mechmerche R, *et al.* Percutaneous valvuloplasty for combined mitral and tricuspid stenosis: results in 3 cases. *Arch Mal Coeur* 1990;83:1585–9.

8 Konugres GS, Lau FYK, Ruiz CE. Successive percutaneous double-balloon mitral, aortic and tricuspid valvotomy in rheumatic trivalvular stenoses. *Am Heart J* 1990;119:663–6.

9 Wren C, Hunter S. Balloon dilatation of a stenosed bioprosthesis in the tricuspid valve position. *Br Heart J* 1989;61:65–7.

10 Chow W-H, Cheung K-L, Tai Y-T, Cheng C-H. Successful percutaneous balloon valvuloplasty of a stenotic tricuspid bioprosthesis. *Am Heart J* 1990;119:666–8.

11 Chen CR, Lo ZX, Huang ZD, Cheng TO. Concurrent percutaneous balloon valvuloplasty for combined tricuspid and pulmonic stenoses. *Cathet Cardiovasc Diagn* 1988;15:55–60.

12 Bourdillon PDV, Hookman LD, Morris SN, Waller BF. Percutaneous balloon valvuloplasty for tricuspid stenosis: haemodynamic and pathological findings. *Am Heart J* 1989;117:492–5.

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CASE REPORTS

Incessant atrial tachycardia accelerated by pregnancy

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Abstract

A 24 year old patient presented with incessant atrial tachycardia during the course of a twin pregnancy. Medical treatment slowed the ventricular response without restoring sinus rhythm. During labour the tachycardia spontaneously reverted to sinus rhythm. Subsequently the same arrhythmia was documented with a slower ventricular response than during pregnancy.

Case report

At 21 weeks' gestation of a twin pregnancy a 24 year old patient was transferred for management of incessant supraventricular tachycardia because of concerns about the effect on placental function. There was a three month history of palpitation and chest discomfort, dizziness, and exertional dyspnoea that had begun eight weeks into the pregnancy. There was no history of viral illness and she had been otherwise healthy with no previous history of palpitation. At admission the heart rate was 200 beats/min and systolic blood pressure was 90 mm Hg. Her electrocardiogram showed a narrow QRS complex tachycardia with upright P waves in the inferior limb leads and V1, with a frontal P wave axis of +90° (fig 1A). The PR interval was 140 ms. Occasionally non-conducted P waves of identical configuration and timing were seen during the tachycardia (fig 1B). The rate of the arrhythmia showed considerable diurnal variability ranging from 135 to 210 beats/min. Isolated ventricular extrasystoles did not reset the tachycardia. There was QRS alternans at ventricular rates faster than 190 beats/min. Haematological studies, urea and electrolytes, and liver function tests were normal. A free thyroxine plasma concentration of 164 nmol/l (normal range 60–140) and thyroid stimulating hormone concentration of 1·4 IU/l (normal range 0·15–3·2) were consistent with pregnancy. Transthoracic echocardiography and chest *x* ray were normal. Fetal echocardiography showed normal hearts and rates.

The arrhythmia did not respond to carotid sinus massage, Valsalva manoeuvres or intravenous verapamil. Digoxin was used without benefit and cardioversion did not restore sinus rhythm or affect the ventricular response rate. Metoprolol and digoxin in combination slowed the ventricular rate to 185 beats/min but the diurnal fluctuation in PP and RR intervals continued. Flecainide was therefore introduced in place of metoprolol and digoxin. This slowed the atrial rate to 115 beats/min and allowed transient episodes of sinus rhythm at 75 beats/min to appear with a frontal P wave axis of +10°. The PR interval was 200 ms with no evidence of pre-excitation (fig 2). This was considered a satisfactory interim result and the patient was discharged on oral flecainide 100 mg three times daily. During the next month the QRS duration increased from 80 ms to 100 ms and the heart rate was never consistently below 130 beats/min on Holter monitoring. Because of this inadequate rate control, flecainide was stopped and amiodarone was introduced at a dose of 800 mg a day for one week and maintained at 400 mg daily. This slowed the heart rate to 110 beats/min. On this treatment, she felt better, but was considerably restricted in her exercise capacity by palpitation, fatigue, and dyspnoea. There was no clinical evidence of heart failure or compromised fetal development.

At 31 weeks' gestation two healthy infants were delivered vaginally by forceps. Sinus rhythm returned spontaneously and the mother's heart rate fell below 100 beats/min during the first stage of labour. After delivery she reported that palpitation had ceased and she remained in sinus rhythm when seen in outpatients two weeks after hospital discharge. Amiodarone was stopped at this time and her electrocardiogram was similar to that in fig 2. The diagnosis was therefore assumed to be pregnancy related atrial tachycardia and this was supported by the prominent left atrial component to the P wave in sinus rhythm. She was re-referred, however, six months after delivery with non-cardiac symptoms at which time an electrocardiogram showed return of atrial tachycardia with a ventricular rate of 115 beats/min. She was on no antiarrhythmic treatment.

Discussion

Pregnancy is frequently associated with sinus tachycardia and increased ectopic activity has

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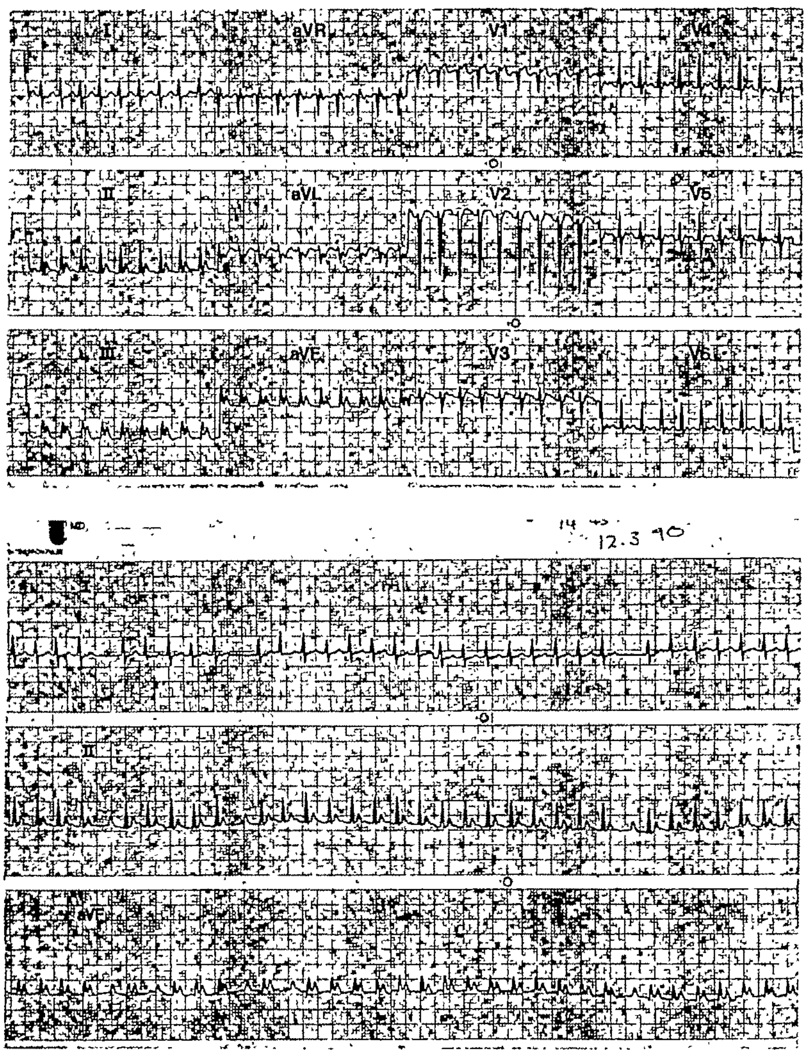

Figure 1 (A) Electrocardiogram showing narrow QRS tachycardia. (B) Rhythm strip showing non-conducted P waves of identical configuration and timing during tachycardia.

been noted both in the atrium and the ventricle throughout pregnancy.[1,2] Paroxysmal supraventricular tachycardia has been seen[1,3,4] and usually occurs in a patient with a history of supraventricular arrhythmias before pregnancy or in a patient with pre-existing rheumatic heart disease.[5] Such arrhythmias usually occur in the third trimester[6] but the true incidence is unknown.[7] Persistent atrial tachycardia such as was present in this patient is uncommon and has rarely been reported during pregnancy.[8,9] It has not previously been seen reverting to sinus rhythm during labour. An automatic atrial tachycardia more typically occurs in childhood[10,11] or complicating heart disease[12] or metabolic upset including digitalis toxicity.[13] In this case, recurrence of the same tachycardia some months later suggests that the patient had a potential for atrial tachycardia unrelated to pregnancy, but which first presented at an accelerated rate during pregnancy.

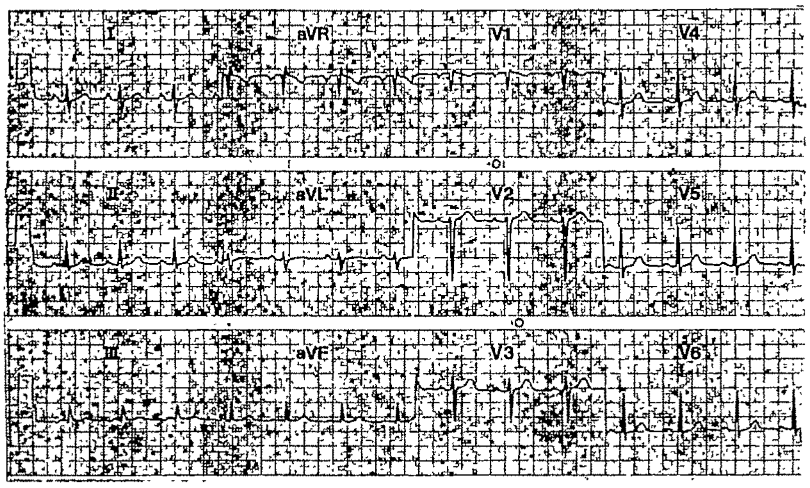

Figure 2 Electrocardiogram after return to sinus rhythm.

The mechanism of the tachycardia in this patient was probably enhanced sympathetic reactivity of an ectopic atrial focus. This accords with the increased plasma catecholamine concentrations and the increased adrenergic receptor sensitivity during pregnancy.[4,14] Increased atrial stretch due to plasma volume enlargement might also be implicated. The possible influence of the high concentrations of oestrogen and progesterone in pregnancy is unknown. An enhanced response to prostaglandins has been reported in pregnancy,[15] and in susceptible patients this could perhaps induce an atrial tachycardia. Thyrotoxicosis could also facilitate atrial arrhythmias; but there was no clinical or biochemical evidence of thyroid overactivity. Why the arrhythmia stopped during labour is not clear.

Because the persistent atrial tachycardia might have caused congestive cardiac failure in our patient[16–18] or have affected placental function and subsequent fetal development[19] we tried to reduce the ventricular rate response when sinus rhythm could not be restored. The management of such arrhythmias in pregnancy is difficult. Verapamil, digoxin, or cardioselective β blockade are appropriate and usually well tolerated.[20,21] Flecainide seems to be safe and cardioversion is not contraindicated.[22] Amiodarone is regarded as an agent of last resort because of concerns about neonatal goitre and its presence in breast milk.[23,24] An alternative treatment is to insert a temporary pacing electrode to terminate the arrhythmia or convert it to atrial fibrillation. Though appropriate radiation protection could be used, pacing was not thought likely to be successful in our patient and we thought that atrial fibrillation might further compromise placental function.

This rare case highlights the risk that inpatients with the potential for atrial tachycardia the condition can be precipitated and accelerated by pregnancy. The arrhythmia was persistent and led to unrealised concerns about placental function but it reverted to sinus rhythm early during labour. Treatment of a persistent tachycardia in pregnancy may be potentially toxic to the mother or fetus or both. Despite a twin pregnancy and incessant supraventricular tachycardia our patient delivered two healthy infants.

1 Mendelson CL. Disorders of the heartbeat during pregnancy. *Am J Obstet Gynec* 1956;72:1268–301.
2 Sullivan JM, Ramanathan KB. Management of medical problems in pregnancy—severe cardiac disease. *N Engl J Med* 1985;313:304–9.

3 Oakley GDG. Pregnancy and heart disease. In: Julian DG, Camm AJ, Fox KM, Hall RJC, Poole-Wilson PA, eds. *Diseases of the heart*. London: Balliere Tindall, 1989: 1363–71.

4 Kay J, Priano LL. Paroxysmal atrial tachycardia during pregnancy. *Anesthesiol Rev* 1987;14:8–15.

5 Szekely P, Snaith L. *Heart disease and pregnancy*. Edinburgh: Churchill Livingstone, 1974:90–101.

6 Perloff JK. Pregnancy and cardiovascular disease. In: Braunwald E, ed. *Heart disease*. 3rd ed. Philadelphia: WB Saunders, 1988:1848–69.

7 Metcalfe J, McAnulty JH, Ueland K. *Burwell and Metcalfe's Heart disease and pregnancy*. 2nd ed. Boston: Little, Brown, 1986:307–35.

8 Proclemer A, Feruglio GA. Tachicardia "sinusale" idiopatica permanente in gravidanza. *G Ital Cardiol* 1988;18:333–8.

9 Hubbard WN, Jenkins BAG, Ward DE. Persistant atrial tachycardia in pregnancy. *BMJ* 1983;287:327.

10 Olsson SB, Blomstrom P, Sabel KG, William-Olsson G. Incessant ectopic atrial tachycardia: successful surgical treatment with regression of dilated cardiomyopathy picture. *Am J Cardiol* 1984;53:1465–6.

11 Keane JF, Plauth WH, Nadas AS. Chronic ectopic tachycardia of infancy and childhood. *Am Heart J* 1972;84:748–57.

12 Haines DE, DiMarco JP. Sustained intraatrial reentrant tachycardia: clinical, electrocardiographic and electrophysiologic characteristics and long-term follow up. *J Am Coll Cardiol* 1990;15:1345–54.

13 Camm AJ. The recognition and management of tachyarrhythmias. In: Julian DG, Camm AJ, Fox KM, Hall RJC, Poole-Wilson PA, eds. *Diseases of the heart*. London: Balliere Tindall, 1989:509–83.

14 Symonds EM. Pregnancy Hypertension. In: Julian DG, Camm AJ, Fox KM, Hall RJC, Poole-Wilson PA, eds. *Diseases of the heart*. London: Balliere Tindall, 1989: 1372–83.

15 Broughton Pipkin F, Morrison R, O'Brien PM. The effect of prostaglandin E1 upon the pressor and hormonal response to exogenous angiotensin II in human pregnancy. *Clin Sci* 1987;72:351–7.

16 Vitale P, de Stefano R, Vitale N, Pisacane C. Disfunzione miocardia conseguente a tachicardia sopraventricolare. *G Ital Cardiol* 1989;19:928–32.

17 Antonelli Incalzi R, Gemma A, Frustaci A, Rossi E, Carbonin PU. Low atrial tachycardia as primary cause of the heart failure complicating congestive cardiomyopathy. *Acta Cardiol* 1989;44:335–9.

18 Cruz FES, Cheriex EC, Smeets JLRM, *et al*. Reversibility of tachycardia-induced cardiomyopathy after cure of incessant supraventricular tachycardia. *J Am Coll Cardiol* 1990;16:739–44.

19 Homans DC. Peripartum cardiomyopathy. *N Engl J Med* 1985;312:1432–7.

20 Metcalfe J, McAnulty JH, Ueland K. *Burwell and Metcalfe's Heart disease and pregnancy*. 2nd ed. Boston: Little, Brown, 1986:367–89.

21 Kendall MJ. Impact of beta 1 selectively and intrinsic sympathomimetic activity on potential unwanted non-cardiovascular effects of beta blockers. *Am J Cardiol* 1987;59:44F–7F.

22 Schroeder JS, Harrison DC. Repeated cardioversion during pregnancy. *Am J Cardiol* 1971;27:445–9.

23 Foster CJ, Love HG. Amiodarone in pregnancy. Case report and review of the literature. *Int J Cardiol* 1988;20:307–16.

24 McKenna WJ, Harris L, Rowland E, Whitelaw A, Storey G, Holt D. Amiodarone therapy during pregnancy. *Am J Cardiol* 1983;51:1231–3.

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Severe rheumatic mitral stenosis with pericardial effusion causing left ventricular tamponade

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Abstract

A woman of 38 was admitted for urgent surgery of severe mitral stenosis causing pulmonary oedema. Echocardiography showed a pericardial effusion with apparent distortion and collapse of the left ventricle. Urgent drainage of the effusion before mitral valve surgery led to an improvement in cardiac output with no detectable change in right heart pressures.

Cardiac tamponade caused by pericardial effusion predominantly affects the right side of the heart, resulting in venous paradox (Kussmaul's sign) and visible compression and distortion of the right ventricle on cross sectional echocardiography.[1] However, in severe pulmonary hypertension tamponade may lead to preferential compression and distortion of the left heart.[2] This effect is attributed to the high right heart pressures or hypertrophy, or both. We report a patient with severe mitral stenosis in whom a moderately sized pericardial effusion led to collapse of the left ventricle, which was visualised by echocardiography, and in whom drainage of the effusion led to an improvement in haemodynamic function.

Case report

A 38 year old woman from Bangladesh was admitted with sudden onset of severe dyspnoea and in a state of collapse. She was unable to give a history but later it became known that she had been breathless on exertion for the previous three years. On examination she had cold and sweaty hands and feet with a blood pressure of 70/40 mmHg, an irregular pulse rate (150 beats per minute), and a respiratory rate of 32 per minute. The chest *x* ray showed pulmonary oedema and an enlarged cardiac silhouette with a configuration that suggested left atrial enlargement. She was urgently intubated and ventilated with intermittent positive pressure ventilation.

The electrocardiogram showed atrial fibrillation with a ventricular rate of approximately 160 beats per minute. Further clinical examination showed a left parasternal heave, very loud first heart sound, accentuated pulmonary second sound, and an early but quiet opening snap with a long and loud diastolic murmur at the apex. M mode and cross sectional echocardiography confirmed the appearance of severe mitral stenosis with an enlarged left atrium and right heart. The patient remained hypotensive with cold extremities and a low urine output of 5 to 10 ml/hour. Swan-Ganz catheterisation showed a mean right atrial pressure of 28 mmHg and a mean pulmonary artery pressure of 78 mmHg; a satisfactory pulmonary wedge pressure tracing could not be obtained.

The cross sectional echocardiogram also showed a moderately sized pericardial effusion with apparent distortion and collapse of the left ventricle in some but not all cardiac cycles. While arrangements were made for urgent mitral valve replacement it was decided to drain the pericardial fluid in an attempt to improve the cardiac output. After 600 ml of serous fluid was removed by subxiphoid pericardiotomy[3] the systemic blood pressure rose to 80/50 mmHg, heart rate fell from 135 to 110 beats per minute in atrial fibrillation, cardiac output determined by thermodilution (Swan-Ganz catheter) improved from 1·8 to 2·6 l/min, and right heart pressures were unchanged.

One hour later mitral valve replacement was performed via a median sternotomy. The native mitral valve was very thickened with rolled edges and fibrotic contraction of the papillary muscles and chordae tendineae: the valve orifice area was approximately 0·5 cm^2. The mitral valve was replaced with a number 27 Björk-Shiley prosthetic valve. At the end of cardiopulmonary bypass the pulmonary artery systolic pressure was 120 mmHg and the systemic arterial systolic pressure 100 mmHg. The patient required inotropic support and ventilation for 48 hours but she subsequently made an uncomplicated recovery.

Discussion

The haemodynamic features of cardiac tamponade are complex and may differ between patients.[4] Animal experiments suggest that right sided cardiac compression contributes more to the haemodynamic derangement than does left heart compression.[2 5] Echocardiographic studies in patients consistently show right atrial diastolic collapse whereas left atrial and right ventricular diastolic collapse are variable findings.[6 7]

Several reports suggest that the clinical and echocardiographic signs of cardiac tamponade may be atypical in patients with pulmonary hypertension and right ventricular hypertro-

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phy. Arterial pulsus paradoxus may be absent, and this has been attributed to increased impedance to the normal inspiratory increase in right ventricular filling.[8 9] Echocardiographic studies show that right ventricular collapse may be absent if right ventricular hypertrophy is severe.[2 10 11] Preferential left atrial compression has been described in such a patient.[12] Preferential compression of the left heart may also occur with loculated pericardial effusions or haematomas.[13]

We are not aware of any previous reports of compression of the left ventricle caused by a generalised pericardial effusion without compression of the other cardiac chambers. The improvement in cardiac output after drainage of the effusion showed the haemodynamic importance of the effusion in this patient. The haemodynamic effects of tamponade with mitral stenosis may differ from those in patients with tamponade and pulmonary hypertension owing to other causes, in whom left atrial diastolic collapse may be important—such collapse was not seen in our case, presumably because left atrial pressure was high.

We are grateful to Dr R Balcon and Mr P Magee for permission to report a patient under their care.

1 Armstrong WF, Schilt BF, Helper DJ, Dillon JC, Feigenbaum H. Diastolic collapse of the right ventricle with cardiac tamponade: an echocardiographic study. *Circulation* 1982;65:1491–6.

2 Leimgruber PP, Klopfenstein HS, Wann LS, Brooks HL. The hemodynamic derangement associated with right ventricular diastolic collapse in cardiac tamponade: an experimental echocardiographic study. *Circulation* 1983;68:612–20.

3 Larrey DJ. New surgical procedure to open the pericardium and to determine the cause of fluid in its cavity. *Clin Chirurg* 1829;38:393.

4 Reddy PS, Curtiss EI, O'Toole JD, Shaver JA. Cardiac tamponade: hemodynamic observations in man. *Circulation* 1978;58:265–72.

5 Fowler NO, Gabel M, Buncher CR. Cardiac tamponade: a comparison of right versus left heart compression. *J Am Coll Cardiol* 1988;12:187–93.

6 Kronzon I, Cohen ML, Winer HE. Diastolic atrial compression: a sensitive echocardiographic sign of cardiac tamponade. *J Am Coll Cardiol* 1983;2:770–5.

7 Singh S, Wann LS, Klopfenstein HS, Hartz A, Brooks HL. Usefulness of right ventricular diastolic collapse in diagnosing cardiac tamponade and comparison to pulsus paradoxus. *Am J Cardiol* 1986;57:652–6.

8 Braunwald E. *Heart disease*. 3rd ed. Philadelphia: WB Saunders, 1988:1495.

9 Frey MJ, Berko B, Palevsky H, Hirshfeld JW Jr, Herrmann HC. Recognition of cardiac tamponade in the presence of severe pulmonary hypertension. *Ann Intern Med* 1989; 111:615–7.

10 Gaffney FA, Keller AM, Peshock RM, Lin J-C, Firth BG. Pathophysiologic mechanisms of cardiac tamponade and pulsus alternans shown by echocardiography. *Am J Cardiol* 1984;53:1662–6.

11 Singh S, Wann S, Schuchard GH, Klopfenstein HS, Leimgruber PP, Keelan MH Jr, *et al.* Right ventricular and right atrial collapse in patients with cardiac tamponade—a combined echocardiographic and haemodynamic study. *Circulation* 1984;70:966–71.

12 Brodyn NE, Rose MR, Prior FP, Haft JI. Left atrial compression in a patient with a large pericardial effusion and pulmonary hypertension. *Am J Med* 1990;8:64N–6N.

13 Kronzon I, Cohen ML, Winer HE. Cardiac tamponade by loculated pericardial hematoma: limitations of M-mode echocardiography. *J Am Coll Cardiol* 1983;1:913–5.

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Rupture of a ventricular abscess after mitral valve replacement

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Abstract

A 65 year old man presented with bacterial endocarditis of the mitral valve. Immediately after mitral valve replacement a valve ring abscess ruptured.

Early surgery should be performed when an intramyocardial abscess is suspected.

There are 1500 cases of infective endocarditis in the United Kingdom each year with an overall mortality of 34%.[1] Despite the greater awareness of bacterial endocarditis and emphasis placed on prophylaxis and early treatment over the past 25 years, surgical treatment is occasionally required. The aortic valve is affected in 42% and the mitral valve in 48% of cases. Bacterial endocarditis of the tricuspid valve is associated with drug addiction. We describe a very rare complication of the disease and discuss the management of myocardial abscess.

Case report

A 65 year old man was admitted acutely confused with a two month history of general debility and weight loss. He was pale, dehydrated, and feverish. A single subungual splinter haemorrhage was seen. The spleen was palpable. A pansystolic murmur consistent with mitral regurgitation was heard.

Initial laboratory results were haemaglobin 7·1 g/dl, total white blood cell count 4·1 × 10^3/l, blood urea 25·1 mmol/l, and serum creatinine 402 µmol/l. The electrocardiogram showed left bundle branch block. The chest radiograph showed moderate cardiac enlargement and blunting of the costophrenic angle. Ultrasound examination of his abdomen showed normal kidneys and a grossly enlarged spleen. Echocardiography showed severe mitral regurgitation and a vegetation on the anterior mitral leaflet. There was no evidence of abscess formation. Blood cultures grew *Streptococcus mutans* sensitive to benzylpenicillin and netilmicin.

The patient was treated with intravenous netilmicin, benzylpenicillin, diuretics, and a blood transfusion. There was initial clinical improvement with resolution of both fever and confusion. Subsequently renal function deteriorated, confusion recurred, and congestive cardiac failure refractory to medical treatment developed. Coronary angiography showed a 70% diameter stenosis of the left anterior descending artery.

Urgent mitral valve replacement was performed eight weeks after admission. At operation the heart was moderately enlarged, with pulmonary hypertension and a large pulsating left atrium. Cardiopulmonary bypass was instituted and myocardial protection achieved with cold crystalloid cardioplegia and moderate hypothermia (28°C). The anterior cusp of the mitral valve was totally flailed because its chordae tendineae were ruptured. Several chordae of the posterior cusp were also ruptured. There were multiple vegetations on the valve. There was an abscess cavity in the posterior part of the annulus extending into the ventricular myocardium. The valve was excised and a 29 mm Carbo-Medic bileaflet prosthetic valve was inserted with 2/0 Ethibond sutures buttressed on Teflon felt pledgets. Posteriorly the sutures were placed to close the mouth of the abscess cavity. In this region, however, the tissues were very thin and friable. The patient was weaned from bypass satisfactorily and required minimal inotropic support (3 µg/kg/min dopamine). Haemostasis was satisfactory and the operation was completed.

Reoperation was required urgently two hours postoperatively because off sudden excessive blood loss. We found that the abscess cavity in the posterior atrioventricular groove had ruptured. Cardiopulmonary bypass was reinstated but attempts to control the haemorrhage failed.

At necropsy the prosthetic mitral valve was found to be well seated and its suture line secure. The left ventricle showed considerable hypertrophy without dilatation. In the postero-lateral wall, lying just below the mitral valve ring, an endocardial performation 0·8 cm in diameter communicated with an epicardial haemorrhage (figure). The intramyocardial defect had the appearance of an abscess cavity. Externally there was an epicardial performation 1·0 cm in diameter.

Histological examination showed that the wall of the intramyocardial cavity was composed of a layer of necrotic myocardial tissue covered by thrombus.

Discussion

Left ventricular rupture as a complication of mitral valve replacement was first reported by Roberts and Morrow.[2] In a published series it reported in between 0·5% and 2% of all mitral valve replacements and was fatal in 75% of these cases. A survery of reports in English found 125 cases.[3] Only one of these showed rupture through the base of a myocar-

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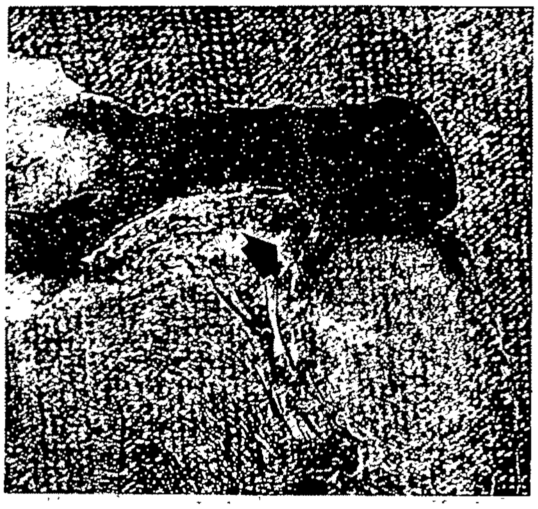

Oblique cut through the lateral part of the mitral valve ring showing the endocardial perforation (arrow) and extensive epicardial haemorrhage.

dial abscess caused by infective endocarditis. Left ventricular rupture is usually attributed to technical steps in the operation or to stretch injury produced by untethering of the left ventricle through removal of the mural leaflet of the mitral valve. Those patients most at risk are generally frail elderly women who have a small ventricular cavity and thin myocardium associated with long-standing mitral stenosis.

There is only one other report of rupture through a ventricular myocardial abscess after mitral valve replacement.[2] Necropsy studies show that valve ring abscesses are a more frequent complication of infective endocarditis affecting the aortic valve.[4] In these cases the myocardial abscess is often associated with infection by *Staphylococcus aureus*, pericarditis, various degrees of atrioventricular block, short duration of symptoms, or new onset of aortic insufficiency. Non-paroxysmal junctional tachycardia and Wenckebach or complete heart block with a QRS of normal width are all consistent with inflammation adjacent to the mitral valve.[5] Abscesses associated with both aortic and mitral valves occur more frequently when the infecting organism is a highly virulent one, such as a pneumococcus or staphylococcus, and occasionally an α streptococci.

Preoperative diagnosis can be difficult. Methods that have been used to detect myocardial abscess formation include echocardiography, computed tomography of the chest, gallium scanning, and ^{111}In platelet scintigraphy. The sensitivity of echocardiography and computed tomography is low.[6] Gallium imaging for endocarditis or abscess formation is not widely used, and scintigraphy with ^{111}In labelled leucocytes has not yet been fully evaluated.

Studies attest to the poor prognosis of patients with myocardial abscess.[4,7] The development of a valve ring abscess is always an indication for prompt surgical intervention with excision of infected material and valve replacement. Without this, and despite appropriate antibiotic therapy, mortality remains high. Annular inflammation and the friability of tissues creates difficulty in seating the prosthetic valve. There is a risk of postoperative valve insufficiency. Early diagnosis of the developing abscess offers the only hope for achieving surgical success.

This case illustrates a rare complication of mitral valve replacement in a patient with infective endocarditis. The grave prognosis of myocardial abscess justifies surgical intervention.

We thank Mr G Keen for permission to publish this report.

1 Schurr LP, Ball AP, Geddis AM, Gray J, McGhie D. Bacterial endocarditis in English in the 1970's. A review of 70 patients. *QJ Med* 1977;46:499–512.
2 Roberts WC, Morrow AG. Cause of early postoperative death following cardiac valve replacement. *J Thorac Cardiovasc Surg* 1967;54:422–43.
3 Karlson KJ, Ahraf MM, Berger RL. Rupture of left ventricle following mitral valve replacement. *Ann Thorac Surg* 1988;46:590–7.
4 Arnet EN, Roberts WC. Valve ring abscess in active infective endocarditis. *Circulation* 1976;54:141–5.
5 Hosea SW. Virulent streptococcus viridans bacterial endocarditis. *Am Heart J* 1981;101/2:174–6.
6 Cerqueria MD, Jacobson AF. Indium^{111} leucocyte scintigraphic detection of myocardial abscess formation in patients with endocarditis. *J Nucl Med* 1989;30:703–6.
7 Weaver JP, Crawford FA, Kratz JM, Sade RM. Valve replacement for native valve endocarditis. *Am Surg* 1984;50:40–2.

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BRITISH CARDIAC SOCIETY

A survey of nuclear cardiological practice in Great Britain

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on behalf of the British Nuclear Cardiology Group

Abstract

There is little information on the practice of nuclear cardiology in Great Britain. On behalf of the British Nuclear Cardiology Group in October 1988 we sent a postal questionnaire to 143 hospitals with nuclear medicine facilities (at least 70% of such hospitals). Sixty nine replies were received (48%), of which 23 (33%) were from teaching hospitals and 46 (39%) non-teaching. In these hospitals 147 904 isotope investigations were performed annually (mean 2311 per centre) of which 17 298 (12%) (mean 254 per centre) were cardiac studies. Of these, 59% were equilibrium radionuclide ventriculograms, 14% first pass ventriculograms, and 27% thallium-201 scans. Rest studies were performed more commonly by radiographers or technicians (63%) than by doctors (20%), but doctors were more commonly involved in stress studies (48%). Radiologists reported the studies more often (28%) than they performed them (6%). Methods of acquisition and analysis were varied and, for instance, the lower limit of normal left ventricular ejection fraction ranged from 35% to 75% (mean 49%). For thallium imaging 42% of centres used dipyridamole in some patients and 24% used tomography.

These data show that nuclear cardiology techniques are used much less frequently in Great Britain than in countries such as the United States and Germany, that the ratio of blood pool to myocardial perfusion imaging is much higher than elsewhere, and that methods are poorly standardised. They may provide the impetus to improve the service and serve as a baseline for future surveys.

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The role of nuclear medicine in patient management is increasing because of the importance of the functional information that it provides.[1] The number of nuclear medicine publications listed in *Index Medicus* has increased rapidly since 1977. At the most recent meetings of the American Heart Association and the European Congress of Cardiology just under 10% of the abstracts reported work with isotope techniques. Thus in both North America and Europe nuclear cardiology is an important area of research and by implication also of clinical practice.

Great Britain seems to lag behind other countries in the adoption of nuclear cardiology, but little objective information is available. In 1983 a postal survey of consultant physicians in Scotland highlighted the poor availability of nuclear cardiology techniques.[2] Since this time, the position in other countries has altered considerably. To obtain information on current practice, we have analysed the results of a postal questionnaire sent on behalf of the British Nuclear Cardiology Group to departments of nuclear medicine and cardiology throughout Great Britain.

Methods

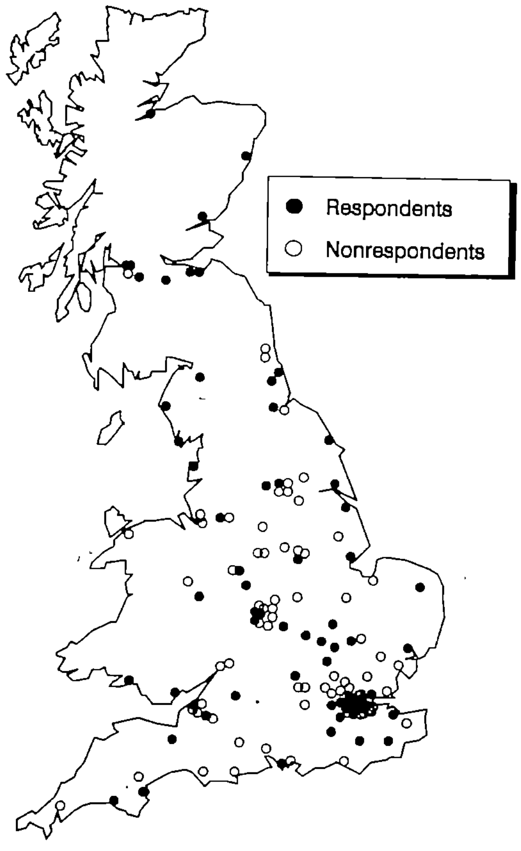
A questionnaire was sent to 143 hospitals known to perform nuclear medicine and the requested completion date was October 1988. The centres were identified from the membership lists of the British Nuclear Cardiology Group, the British Nuclear Medicine Society, the British Cardiac Society, and the Hospital Physicists Association, with cross referencing from the service lists of the major manufacturers of gamma cameras and nuclear medicine computers supplying the British market. While this is a small fraction of the hospitals in the country (total approximately 3000), it included all regional cardiac centres and most district hospitals providing a nuclear medicine service. Not every question was answered and the results are expressed as a percentage of the number of replies received.

Results

GENERAL RESPONSE AND STUDY NUMBERS

Sixty nine replies (48%) were received. Of these, 23 (33%) were teaching hospitals with a similar percentage of teaching hospitals in the non-responders (29 of 74 (39%)). The proportion of teaching and district hospitals was therefore representative of the survey group as a whole ($\chi^2 = 0{\cdot}31$, p = NS). The figure shows the geographical distribution of the respondents and non-respondents.

The respondents' definition of their departments was used. The largest proportion of replies was from departments of nuclear medicine (40%), followed by medical physics



Map indicating the site of all centres that were circulated and whether a response was received to the questionnaire.

(26%), radiology (20%), and cardiology (11%). Departments of cardiology were more commonly represented among the teaching hospitals than the district general hospitals (χ^2 = 6·8, p = 0·009), and departments of radiology or medical physics were more common among the district hospitals (χ^2 = 7·2, p = 0·007). Research studies were performed in addition to routine clinical work in 78% of departments of cardiology, 65% of medical physics, 52% of nuclear medicine, and 22% of radiology. Research was significantly more common in teaching hospitals, being performed in 20 of the 21 teaching hospitals but only seven of the 28 district hospitals that replied (χ^2 = 23·9, p = 1·0 × 10^{-6}). Thus the repondents were polarised between research based departments of cardiology in teaching hospitals and clinically based departments of radiology or medical physics in the district hospitals.

Table 1 shows the number of studies reported. Fifty (74%) of 68 centres performed cardiac studies, and 11·7% of all nuclear medicine studies reported were cardiac. These numbers are similar to ones reported in a recent survey of general nuclear medicine departments,[3] where cardiac studies accounted for 11% of the workload. Teaching hospitals performed a significantly higher percentage of cardiac studies (16%) than district hospitals (7%) (χ^2 – 20·7, p = 5·4 × 10^{-6}), in keeping with the higher number of departments of cardiology represented in the teaching hospitals. Table 2 shows the distribution of types of cardiac study. Sixty four per cent of centres performed no first pass radionuclide ventriculography and 20% performed no thallium-201 scintigraphy. Thus in most centres equilibrium radionuclide ventriculography made up at least half of the workload with a variable proportion of thallium-201 scintigraphy.

Respondents were asked to assess trends in their workloads. About half the centres (53%) reported that their general imaging workload was increasing and slightly more (57%) that their cardiac workload was increasing. A comparison of trends with absolute workloads shows significant associations (table 3). For general nuclear mecicine, there was a significant tendency for small departments (up to 2000 studies per year) to report a rising trend (χ^2 = 4·25, p < 0·05), but for cardiac investigations this situation was reversed. Smaller centres (up to 150 cardiac studies per year) were more likely to report a static or falling trend (χ^2 = 6·57, p < 0·02).

The median proportion of patients studied as outpatients was 80%, confirming that nuclear cardiological investigations are usually outpatient procedures. Over 70% of centres reported that their most frequent referral source was a cardiologist. Of the 46 (67%) centres providing full data on referral pattern, 73% of all cardiac studies were requested by cardiologists, 16% by other physicians, and 11% by surgeons including cardiac surgeons.

EQUIPMENT AND STAFF

The mean number of cameras per centre was 1·8 (median 1, maximum 7). Mean camera age was 5·2 years (median 5, maximum 10). Teaching hospitals had almost twice as many cameras as district hospitals (mean 2·7 and 1·4 per centre), although camera age was similar (mean 5·2 and 5·2 years respectively). Each camera most commonly performed between 500 and 1500 studies per year. The percentage of centres according to camera load was <500 studies per camera = 5%, 501–1000 studies = 35%, 1001–1500 = 38%, 1501–2000 = 17%, >2001 studies per camera = 5%.

The staff groups who performed and interpreted studies varied widely (table 4) confirming the diversity of nuclear cardiological prac-

Table 1 Annual workload of imaging procedures (first pass radionuclide ventriculography, equilibrium radionuclide ventriculography, and thallium-201 myocardial perfusion imaging

Data	*All isotope studies*	*First pass rest*	*First pass stress*	*Equilibrium rest*	*Equilibrium stress*	*Thallium*
Number of replies	64	67	66	64	64	66
Percentage performing studies	95	28	3	72	41	64
Total studies	147 904	1474	1010	8080	2132	4602
Mean studies per centre	2425	78	505	176	82	110
Maximum number in any centre	8900	500	1000	1400	500	1500

Table 2 Number of hospitals according to the proportion of nuclear cardiology studies performed. Only 50 hospitals from which a reply to all three questions was received are included

Percentage	*First pass RNV*	*Equilibrium RNV*	*Thallium-201*
0	32	2	10
1– 10	10	2	4
11– 20	1	3	6
21– 30	2	2	3
31– 40	2	7	6
41– 50	2	10	5
51– 60	0	3	5
61– 70	0	3	4
71– 80	0	5	3
81– 90	0	4	1
91–100	1	9	3

RNV, radionuclide ventriculography.

Table 3 Association between trends and annual workload

	Centres with rising case load	*Centres with static or falling case load*
Total studies:		
1–2000	21	11
>2000	10	16
Cardiac studies:		
1–150	12	17
>150	17	5

tice in Great Britain. In almost all centres, staff from several groups were involved at all stages. Rest studies were performed more commonly by radiographers or technicians (63%) than by doctors (20%), but doctors were more commonly involved in stress studies (48%). Radiologists reported the studies more commonly (28%) than they performed them (6%). In 64% of centres, reporting was performed by doctors only, in 34% it was by a group that included doctors, and in one centre reporting was performed by non-medical staff.

FIRST PASS RADIONUCLIDE VENTRICULOGRAPHY

First pass radionuclide ventriculography was the least common (14·4%) of the three major cardiological investigations. Of 18 centres performing such studies, two used a multicrystal gamma camera and the remainder a single crystal camera. The most common reason for performing the studies was to evaluate intracardiac shunting (47%), though it was also used to evaluate left (23%) and right (17%) ventricular ejection fractions.

EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Equilibrium radionuclide ventriculography was the commonest study performed, accounting for more than half (59%) of all cardiac studies. Some form of stress was used in 35 (61%) of the 57 centres that performed radionuclide ventriculography: of these, 66% used dynamic exercise, 9% isometric exercise, 20% cold pressor stress, and 5% pharmacological stress. Thirty four per cent of centres routinely withdrew cardiac medication before stress radionuclide ventriculography, 30% did not, and 34% gave a qualified answer, such as that it depended on the requesting physician.

Table 4 Number of centres according to the type of staff involved in cardiac procedures (more than one person may be involved)

	Rest study	*Stress study*	*Reporting*
Cardiologist	9	26	17
Nuclear physician	3	13	18
Radiologist	3	6	22
Physicist	13	12	20
Radiographer	19	10	1
Technician	28	26	2

In vivo erythrocyte labelling was the most common (76%) form of labelling, followed by semi in vitro (14%), human serum albumin (6%), and in vitro (4%). The commonest dose of technetium-99m was 740 MBq given in 31% of centres followed by 800 MBq in 19%. Nineteen per cent of centres gave doses of less than 500 MBq. All centres imaged in the left anterior oblique projection (or a modification) but, in addition, 51% imaged in the anterior projection, 28% in the right anterior oblique projection, and 11% in the left lateral projection. The commonest number of frames acquired per cardiac cycle was 16 (39%), 22% of centres acquired 20 frames, 17% acquired 24 frames, and 4% acquired 32 frames.

Nearly all centres analysed the studies to provide left ventricular ejection fraction (92%) and left ventricular wall motion (84%), but right ventricular ejection fraction (14%) and valve regurgitation (14%) were also sometimes measured. Fourier analysis was the commonest method of assessing wall motion (88%). For the calculation of background, the respondents showed preferences for a horseshoe shaped region of interest (63%), a single left ventricular region of interest rather than two regions (64%), and manual rather than automatic delineation of regions of interest (57%). Many centres thus prefer the manual methods of analysis to more complex automated methods.

One of the most striking findings of the study was the variation in the normal range for left ventricular ejection fraction. The lower limit had a median value of 50% (range 35–75%) and the upper limit a median of 100% (range 50–100%). Just over half (53%) of the respondents specified no upper limit. Four centres believe that the left ventricular ejection fraction should be at least 60% and three centres believe that this would represent abnormally increased function. The median lower limit of left ventricular ejection fraction was the same (50%) for centres using either one or two left ventricular regions of interest.

THALLIUM-201 MYOCARDIAL PERFUSION IMAGING

Thallium-201 scintigraphy represented 26·6% of all cardiac studies. Dynamic exercise was the commonest method of stress (62% of centres). Intravenous dipyridamole was used in 22% of centres, oral dipyridamole in 7%, and a combination of exercise and dipyridamole in 9%. Planar imaging was the most common technique (70%), followed by emission tomography (23%) and electrocardiogram gated imaging (7%). All centres performing tomography used rotating gamma cameras. Larger departments (more than 50 thallium studies per year) were more likely to use tomography than smaller departments

Table 5 Other cardiac studies

	Number of centres
Indium-111 white cells	9
Technetium-99m pyrophosphate	8
Technetium-99m isonitriles	7
Gallium-67 citrate	7
Non-imaging probe	6
Labelled fatty acids	2
Antimyosin antibody	2
Gold-195m	1
Meta-iodobenzylgluanidine (MIBG)	1

($\chi^2 = 5{\cdot}5$, $p = 0{\cdot}02$), and there was also a tendency that did not achieve statistical significance for teaching hospitals to be more likely to use tomography ($\chi^2 = 3{\cdot}1$, $p = 0{\cdot}077$).

The commonest doses used were 80 MBq (33%) and 74 MBq (29%) and four centres (10%) used more than 80 MBq. The delay time between stress and redistribution images varied from two to five hours (median four), and no centre routinely imaged after five hours. A few respondents used quantitative analysis (43%) or washout analysis (26%), but quantitative analysis was more common in teaching hospitals than district hospitals ($\chi^2 = 3{\cdot}0$, $p = 0{\cdot}085$).

OTHER STUDIES

Very few centres performed other forms of cardiac imaging (table 5). In most cases the number of such studies performed at any centre was low.

Discussion

The aim of this study was to obtain a representative view of the practice of nuclear cardiology in Great Britain. While such a study is unlikely to be complete, we believe that we have achieved our aim. We estimate that about 200 hospitals in Great Britain have at least one gamma camera. Thus we requested information from 70% of centres performing nuclear medicine and, although the response rate was relatively low, there was no bias towards either teaching hospitals or district general hospitals in the responders compared with the non-responders. The geographical distribution of the two groups was similar.

By extrapolation from the 48% response rate, we estimate that the annual rate of nuclear medicine procedures reported was approximately 6000 per million population per year. The rate of nuclear cardiological investigation was 700 per million per year. In the United States in 1985, the rates for general nuclear medicine and nuclear cardiology were 29 600[4] and 3550 per million per year[4] respectively. In 1988 this last figure had increased to 4000 per million per year.[5] Thus five times as many procedures are performed in the United States as in Great Britain, though the proportion of nuclear cardiology to general nuclear medicine is similar. This survey cannot indicate the reason for this difference, but it does allow some informed guesses to be made.

The number of hospitals with suitable equipment is clearly an important factor. In the United States in 1983 it was estimated that approximately half of the hospitals had nuclear medicine facilities[6] whereas the proportion in Great Britain is approximately one third, even in 1990. Median camera age in Great Britain is five years with some centres having 10 year old cameras. Given the rapid advances in camera and computer design this equipment is relatively old, suggesting a low level of capital investment. One effect of the shortage of modern cameras is the low percentage (23%) of centres performing thallium-201 emission tomographic imaging. Although the debate about the relative accuracies of planar and tomographic thallium-201 imaging continues, the tide has turned in favour of tomography. A potent factor in persuading clinical cardiologists to use myocardial perfusion imaging is their familiarity with the images and the ease of interpretation. Tomographic imaging, if well performed is better than planar imaging in these respects and its scarcity may be one reason for the low use of myocardial perfusion imaging.

A second point highlighted by the survey that may explain the difference in nuclear cardiology practice between Great Britain and the United States is the diversity of staff that perform studies. Little formal medical training in nuclear medicine is available in Great Britain. There are eight full-time registrars in nuclear medicine, eight senior registrars, 29 consultants, and six senior lecturers or professors. Most departments are not run, therefore, by full-time nuclear medicine physicians and a very wide range of skills are used. Technicians and radiographers most commonly perform rest studies and cardiologists most commonly perform stress studies. In contrast, radiologists least commonly perform rest or stress studies but most commonly report them. The relatively large number of centres in which cardiologists perform stress studies is encouraging but the fact that they are less commonly involved in reporting is disappointing because the report is most likely to be clinically relevant if formed in close collaboration with the referring clinician. Many cardiologists hold regular meetings where the results of their patients' investigations are reviewed with the relevant clinical staff. Such a setting would be ideal for the reporting of nuclear cardiological procedures.

Apart from differences in the availability and practice of nuclear cardiology, other factors will clearly influence the relative rates of investigation in Great Britain and the United States. These include a more aggressive style of investigation and treatment in the United States, a greater awareness of potential litigation, and different mechanisms of financing medical care. For these reasons, the comparison between countries should not be taken too far.

In addition to the low use of nuclear cardiology, we have identified large discrepancies in practice throughout Great Britain. A particularly worrying finding is the disparity in normal ranges for left ventricular ejection fraction, with the lower range of normal varying from 35% to 75%. It is not known whether this is the result of different perceptions of normality, differences in analytical technique, or technical errors. Clearly, it is important that values are transferrable between centres and this finding should serve as a spur to the standardisation of methods of acquisition and analysis. One of the most potent sources of variation is the estimation of background counts. The commonest method was to use a manually defined horseshoe region of interest lateral and inferior to the left ventricle with a single left ventricular region of interest. This method seems to be the most reproducible, but a greater degree of standardisation is required. It is also surprising to find that most centres use projections in addition to the one that best separates the left and right ventricles in equilibrium radionuclide ventriculography. Acquisition in only a single projection gives a distorted view of the left ventricle with weighting towards the anterior part of the blood pool because of attenuation of counts from the more distant inferior portion.[7] In an attempt to overcome the problem, 79% of centres also image in the anterior or right anterior oblique projections. The reliability of these projections is questionable because of the overlying right ventricle, and the left lateral or left posterior oblique projections are preferable.

For the analysis of wall motion 67% of centres used Fourier phase and amplitude imaging rather than alternative methods such as those based in the motion of contours. This is encouraging because objective measurements of phase and amplitude should aid standardisation. The assessment of contours is not ideal because of its subjectivity and the fact that only the motion of walls seen end-on can be assessed from a contour display.

It is particularly disappointing that 29% of centres used either isometric stress or cold pressor stress to assess left ventricular function during stress. Neither of these techniques is adequate to provoke abnormalities in patients with coronary artery disease though new wall motion abnormalities are highly specific.[8–10]

There was understandably less variation in technique for thallium-201 scintrigraphy but the major finding was that only one quarter of centres used emission tomographic imaging. The strengths and usefulness of emission tomography have already been discussed. There was a significant tendency for larger centres to perform tomography. While it is tempting to speculate that the better quality of tomograms prompts more referrals, an alternative explanation is that only the larger centres have suitable equipment.

Although there was general agreement on the dose of thallium-201, four centres routinely use a dose higher than that recommended by the Administration of Radioactive Substances Advisory Committee (80 MBq). There is increasing pressure to use higher doses in order to obtain good quality tomograms and to allow redistribution imaging at later times. No centres reported redistribution imaging later than five hours after the injection of the isotope, but since the date of the survey evidence has emerged that imaging at four hours can underestimate the extent of viable myocardium.[11] Perhaps it would be better to repeat imaging after a further injection of thallium-201 at rest rather than to study late redistribution. This of course increases the radiation burden to the patient, but doses of 120 to 160 MBq are becoming accepted practice in the United States.[12] The large effective dose equivalents (37·5 to 50 mSv) must be weighed against the potential benefits.

In conclusion, we found that nuclear cardiology investigation is less often used in Great Britain than would be expected by extrapolation from data on some other countries. We have highlighted some practical aspects that may explain the discrepancy, and we believe that the position is unlikely to change without an increase in the number of cardiologists and physicians with experience in nuclear cardiology. This is most likely to come about through undergraduate and postgraduate education and we agree with proposals for a new training programme for cardiology including the statement that "trainees must now acquire not only clinical skills but also considerable expertise in . . . nuclear cardiology."[13]

We are grateful to all respondents who completed the questionnaire. We apologise to any centres that would have been eligible but did not receive a questionnaire. We are anxious to hear from them so that future surveys may be more complete.

1 McAfee JG, Kopecky RT, Frymoyer PA. Nuclear medicine comes of age: its present and future roles in diagnosis. *Radiology* 1990;174:609–20.
2 McKillop JH, Tweddel AC. Physicians' attitudes to nuclear cardiology. *Nucl Med Commun* 1983;4:342–7.
3 Williams ED, Harding LK, McKillopp JH. A postal survey of quality assurance in nuclear medicine imaging in the UK during 1988. *Nucl Med Commun* 1989;10:181–9.
4 Subcommittee of the Health and Environment Research Advisory Committee, Office of Energy Research, US Department of Energy. *Review of the Office of Health and Environmental Research Program, nuclear medicine, 1989.* Washington DC: US Department of Energy, 1989.
5 Ritchie JL, Cerqueira MD. Single photon emission computed tomography (SPECT): 1989 and beyond. *J Am Coll Cardiol* 1989;14:1700–1.
6 McPhee SJ, Garnick DW. Imaging the heart: cardiac scintigraphy and echocardiography in US hospitals (1983). *J Nucl Med* 1986;27:1635–41.
7 Underwood SR, Walton S, Laming PJ, Ell PJ, Emanuel RW, Swanton RH. Differential sensitivity of radionuclide ventriculography for the detection of anterior and inferior infarction. *Br Heart J* 1988;60:411–6.
8 Jones RI, Lahiri A, Cashman PMM, Dore C, Raftery EB. Left ventricular function during isometric hand grip and cold stress in normal subjects. *Br Heart J* 1986;55:246–52.
9 Northcote RJ, Cooke MBD. How useful are the cold pressor test and sustained isometric handgrip exercise with radionuclide ventriculography in the evaluation of patients with coronary artery disease? *Br Heart J* 1987;57:319–28.
10 Findlay IN, Gillen G, Cunningham AD, Elliott AT, Aitchison T, Dargie HJ. A comparison of isometric exercise, cold pressor stimulation and dynamic exercise in patients with coronary heart disease. *Eur J Cardiol* 1988;9:657–64.
11 Yang LD, Berman DS, Kiat H, *et al*. The frequency of late reversibility in SPECT thallium-201 stress-redistribution studies. *J Am Coll Cardiol* 1990;15:334–40.
12 Botvinick EH. late reversibility: a viability issue. *J Am Coll Cardiol* 1990;15:341–4.
13 Joint Training and Manpower Group representing the Specialty Advisory Committee and the Cardiology Committee of the Royal College of Physicians of London, and the British Cardiac Society. Proposals for a new training programme for cardiology. *Br Heart J* 1990;63:317–20.

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BRITISH CARDIAC SOCIETY NEWSLETTER

We had anticipated having some firm news this month about our proposed valve registry (in conjunction with the Society of Cardiothoracic Surgeons) but our plans for a degree of cooperation with the manufacturers have had a setback. Professor Ken Taylor attended a board meeting of the International Association for Prosthesis Manufacturers (APM) in Amsterdam in December to present to them the proposals for the UK valve scheme that we believe might be a pilot for a wider European plan. He has told us the disappointing result of this meeting: "After considerable discussion it became apparent the IAPM members were unwilling to provide any financial support for the initiative. IAPM members believed it was more appropriate for themselves to pursue the development of a standard pan-European registration card of implanted valves, and they considered this approach as their priority. Although a pan-European scheme is welcome—and one that we ourselves have supported in principle—most European countries do not have the level of data registration on valve patients compared with the comprehensive information available through the United Kingdom Valve Registry. The IAPM scheme offers no real prospect of increasing the minority of patients who currently receive a card with details of the implanted valve(s), and therefore it seems important for us to pursue alternative funding approaches in this country." We hope soon to have news of better progress in this area that we identified as a priority very many months ago.

A working party on radiation hazards in cardiology has been set up by the society. Radiation has always been a problem, but two factors are making it more pressing. The first follows from the increasingly complex procedures that are needed in interventionalist cardiology, in electrophysiology, and in paediatric cardiology. Inevitably these lead to longer screening times than are needed for simple angiography. Advances in other imaging techniques—notably echocardiography—are an important mitigating factor, but some cardiologists are facing longer screening times than has been usual, and indeed longer times than may be desirable. The second factor may become increasingly important over the next few years: we face a major reduction in the number of career registrars and research registrars and inevitably this will increase the workload of more senior colleagues in relation to investigation and pacemaker implantation. Clearly there are implications for safety and indeed for staffing levels. The working party will be chaired by John Camm. We are delighted that three distinguished cardiac radiologists have agreed to help: John Reid from Edinburgh, Peter Wilde from Bristol, and Maurice Raphael from London. The other cardiologists are Shakel Qureshi, Martin Rothman, Malcolm Clarke, and Roger Boyle.

We continue to be concerned by the severe problems over staffing faced by cardiologists in the United Kingdom. An important aspect is the impossibility of providing a comprehensive service within our district hospitals. This is faced most acutely by single handed cardiologists in the larger districts. We have written to all who are in this situation (having district populations over 250,000), enclosing an informal questionnaire that was drawn up in cooperation with the President of the Royal College of Physicians who shares our concern. The results will be made available to the college and may be used in the evidence submitted to an enquiry on medical manpower within the National Health Service.

We feel a little guilty (only a little) about the number of questionnaires we are sending out. Accurate information is a powerful weapon. It is essential in our struggle for the facilties to provide an adequate service in the specialty. The staffing surveys for consultants and senior registrars (1991) are nearing completion, and in February we sent out the survey on facilities (1992). For the first time we cooperated with the affiliated groups and incorporated new questions at their request. We also combined forces with the Society of Cardiological Technicians which was intending to conduct its own survey. Their document, which was mailed with our own, is intended for completion by senior or chief technicians. The cooperation will avoid the need to collect information twice. We hope colleagues appreciate that the big bang strategy for surveys—whereby most come in one fell swoop—does save time, trouble, and irritation in the end. Those who put the documents to one side are also aware of the relentless nagging that ensues: it is easier to complete them at once. One of the authors of this letter wishes to report that his was the first completed return for the staffing survey: it did come and go by post, though the University of Sussex is not far away . . .

John Birkhead, in collaboration with colleagues in Bath, Brighton, Doncaster, Merthyr Tydfyl, and Telford, has completed a preliminary study of factors influencing the delay between the onset of symptoms and administration of thrombolytic therapy in patients with acute myocardial infarction. The results, shortly to be submitted for publication, have stimulated much discussion within the audit committee and the project is to be expanded to include 25 cardiac care units in district general hospitals as an exercise that should enable participating centres to compare their performance with that of others. Data collection will be extremely simple, requiring minimal additional work easily incorporated into the routine of the busiest cardiac care unit. If you think you might like to participate please contact John Birkhead at Northampton General Hospital. The second project currently in progress is David de Bono's Confidential Enquiry into Complications from Cardiac Catheterisation (CECCC). Its feasibility was assessed in five cardiac catheterisation laboratories and the study has now been extended to include more than 25 centres. In most centres a senior CCU nurse is responsible for reporting complications: data collection has been remarkably smooth. Interest is maintained by a monthly newsletter and periodic feedback to participants who can identify the results from only their own centre. Such feedback has already identified a consistent pattern of complications in two centres resulting in an internal review of procedures. Ideally we feel that all cardiac centres should participate and if you think you might be prepared to join the next wave please contact David de Bono at Leicester. New audit proposals under discussion relate to non-cardiac surgery in patients on long-term anticoagulant therapy (Mark Dancy) and the management of cardiac surgical waiting lists (Tom Treasure and Michael Joy). We hope that the committee will shortly have control of its own budget. If you have an idea for an audit project requiring national rather than local organisation write to Nick Brooks at Wythenshawe Hospital, Manchester.

We have received news of the British Pacing and Electrophysiology Group from Richard Sutton who writes "BPEG's next annual general meeting will be on 10 July at the Royal College of Physicians, the guest speaker will be Professor Giorgio Feruglio. BPEG continues its educational efforts to combat the inappropriately low rate of pacemaker implantation in the United Kingdom, with symposia in Maidstone, Plymouth, Aberdeen, Liverpool, and Norwich. An educational session is planned for 26 May (2.00 to 5.00 pm) in association with the British Cardiac Society annual meeting in Harrogate. Additional information can be obtained from BPEG (071 351 8298). The working party report on pacemaker prescription that was published in the *British Heart Journal* in August 1991 has attracted 9500 reprint requests so far."

The European Society of Cardiology has published the latest figures on the number of cardiologists in 10 countries who have been elected to the fellowship. Our efforts to promote enthusiasm have not been in vain. To our considerable surprise, the United Kingdom heads the list with 64 fellows, with Italy second at 53. Nevertheless, we are not satisfied that colleagues are availing themselves of the opportunity for support from the British Cardiac Society. We have 390 cardiologists in the United Kingdom at the last count, and many cardiac surgeons in addition. Many more qualify for the fellowship than have applied. The criteria set by the European Society are set out in the newsletter of February 1991. Application forms can be obtained from: ESC Fellowship Department, 22 Rue Juste Olivier, CH-1260 Nyon, Switzerland.

The date of the first teach-in, on molecular biology (Sir David Weatherall), on 31 March is rapidly approaching. By this time all places may well have been taken but we do plan a reserve list so it may be worth telephoning the society if you have not already done so. Abstracts for the first meeting of the European Resuscitation Council (Brighton, 20 and 21 November) are due to be submitted by the end of April. Information packs are available from the British Cardiac Society. Because the society played a key role in the formation of the council we hope to see a good British presence and strong participation.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
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NOTICE

1992

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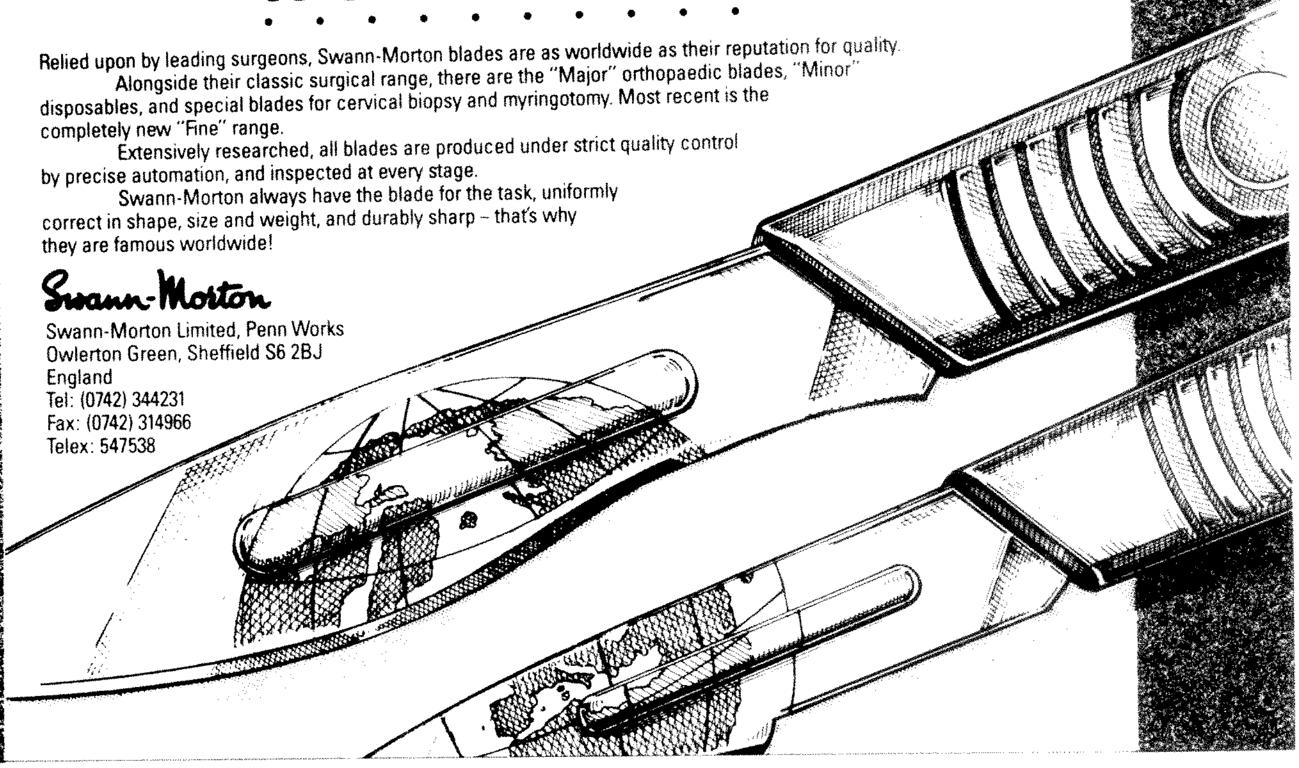

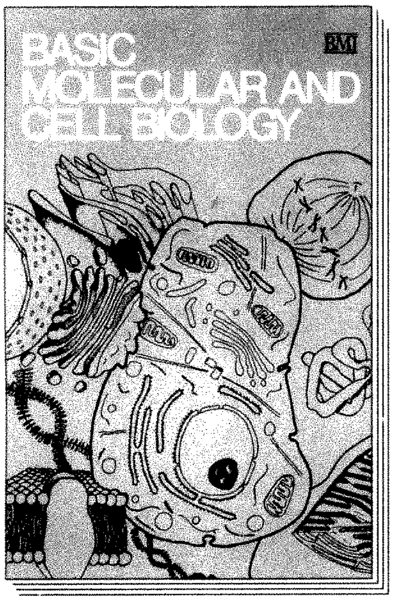
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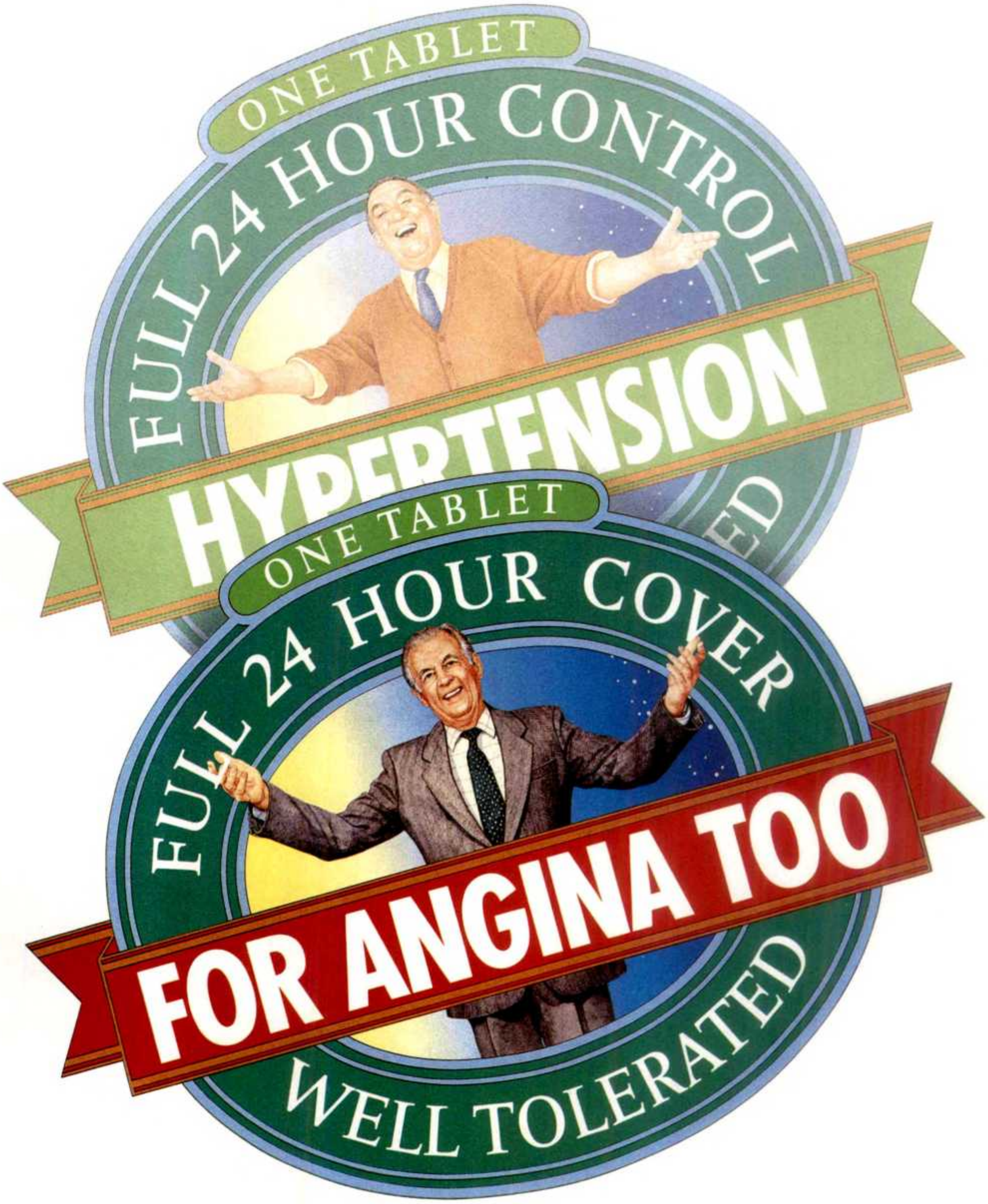

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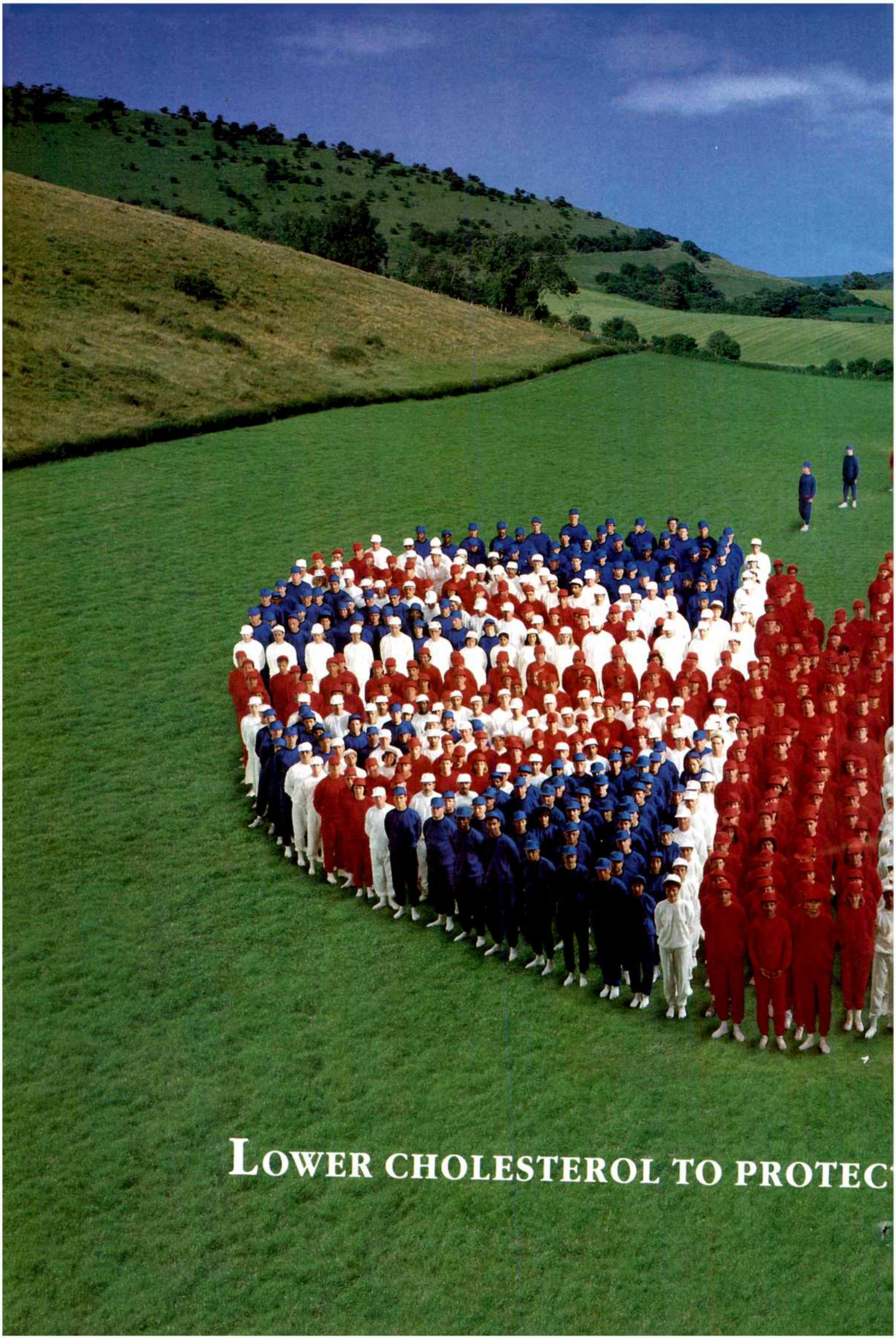
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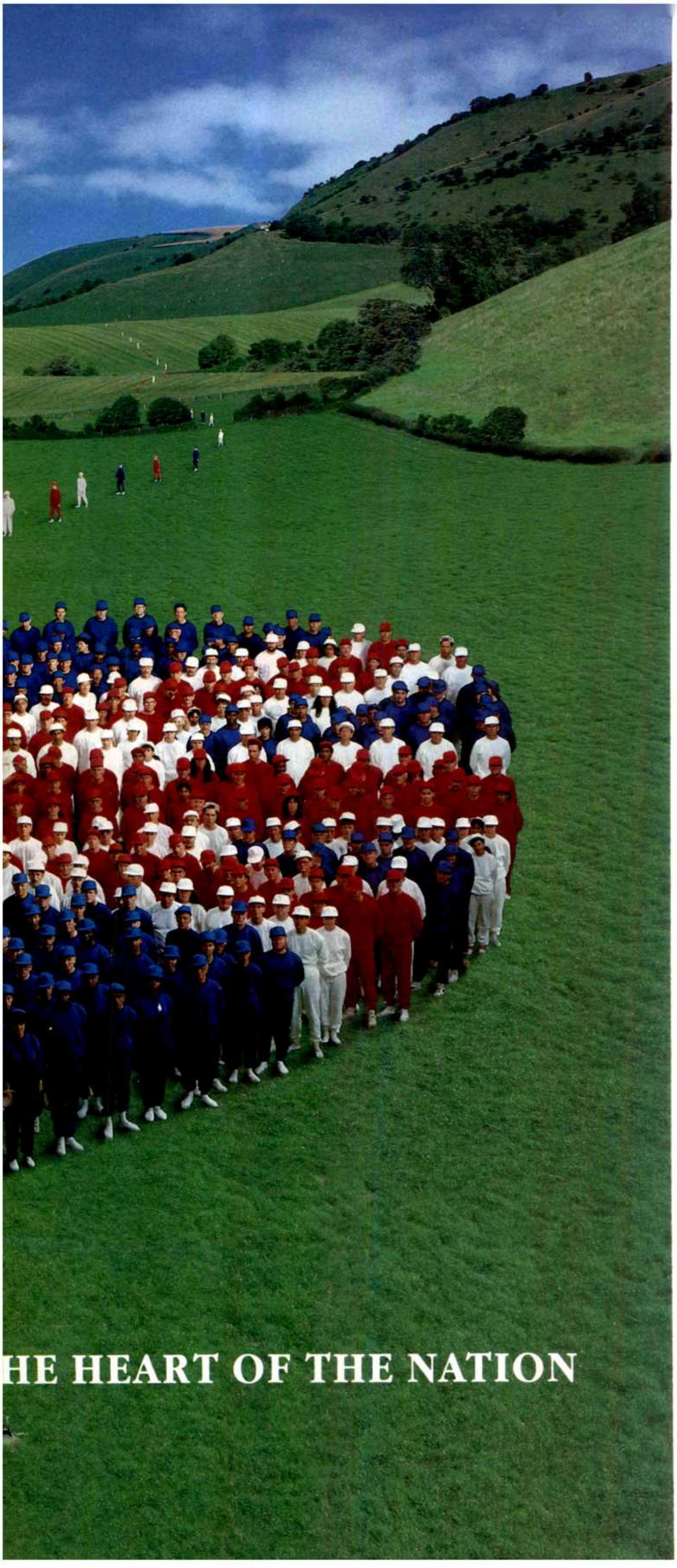
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Product licence numbers: 10 mg tablets, 0025/0241.
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REFERENCES
1. OPCS Monitor DH2. June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

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Br Heart J 1992;67:279–80

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Editorial

Stress proteins, self defence, and the myocardium

Despite advances in the treatment of coronary artery disease, the search for ways to preserve myocardium threatened by ischaemic or reperfusion injury continues. A group of proteins known as the heat shock or stress proteins represent the cell's innate ability to protect itself. Do these proteins have a role in protecting the heart in coronary artery disease and can this self preservation mechanism be exploited therapeutically?

Heat shock proteins were originally described in the 1960s[1] and over the next two decades the concept of thermotolerance developed. It was discovered that cells and organisms exposed to sublethal hyperthermia synthesised stress proteins[2] and were rendered tolerant or resistant to subsequent hyperthermic stress. This group of inducible stress proteins is phylogenetically well preserved, being present in various organisms from bacteria to humans.[3] It is unlikely that their expression in mammals is merely an evolutionary remnant of little relevance to homoeothermic animals, since their induction is not confined to the stimulus of heat. Other stimuli include various metabolic stressors such as cellular hypoglycaemia, reactive oxygen species (hydrogen peroxide and superoxide), and ischaemia[4 5]—all factors that suppress the synthesis of other cellular proteins.

Animal studies have shown that after preconditioning with a brief period of ischaemia the heart is temporarily protected from further ischaemic episodes,[6] and recent evidence suggests that this phenomenon also exists in humans.[7] In addition, a constitutively (basally) expressed stress protein of the 70 kDa heat shock protein (HSP70) family is selectively inducible in rabbit heart by ischaemia.[5]

It is well recognised that heat shock and the subsequent synthesis of stress proteins is protective;[8] whether stress proteins contribute to myocardial preconditioning remains controversial. Attention to date has focused on the 70 kDa stress protein, which has been well reviewed.[8 9]

A role for stress proteins in myocardial preconditioning was supported by work that showed that rendering animals hyperthermic (thus inducing the heat shock protein response) before an episode of cardiac ischaemia had a protective effect both during the ischaemic period and on restoration of perfusion.[10 11] However, a few minutes of myocardial ischaemia has been shown to exert a protective effect, preconditioning the heart against subsequent ischaemic episodes.[6 7] Such a time course suggests that this preconditioning effect is unlikely to be due to stress protein induction: increased expression of HSP70 mRNA is not seen in rabbits until an hour after a short ischaemic period, and an increase in the stress protein itself is only detected after two hours, peaking at 24 hours.[5] In addition, it has been shown that protein synthesis is not a prerequisite for preconditioning.[12]

A further group of stress proteins may contribute to the myocyte's defences. The glucose-regulated stress proteins are induced by cellular hypoglycaemia, a state that occurs during ischaemia when the synthesis of other proteins is suppressed.[13] Though little is known of their functions, they may modulate the response of the myocyte to hypoxia, perhaps by regulating the folding and assembly of proteins disrupted by hypoxia.[14]

Stress proteins also seem to have a role in myocardial adaptation (by hypertrophy), to haemodynamic overload.[15] Cardiomyocytes adapt rapidly to pressure overload with increased protein synthesis. Though the bulk of such proteins comprise contractile units, increased expression of the HSP70 gene is detected as early as an hour after the onset of pressure overload, followed by the appearance of the HSP70 protein. This induction is a short-lived phenomenon; concentrations of HSP70 mRNA return to baseline after 24 hours despite continuous pressure overload. Although the transience of their induction suggests that stress proteins are not the sole cause of compensatory hypertrophy, their perinuclear distribution implies that they may have a permissive role in mediating overload-induced hypertrophy. By the mechanisms discussed below they may permit the rapid recovery of protein synthesis interrupted by the onset of overload, thus enabling the cell to survive the initial stress and to adapt by hypertrophy to continued overload.

What are the mechanisms by which stress proteins provide protection? It has been hypothesised that they recognise and repair hypoxia-induced damage to cellular proteins;[14 16] rescue protein synthesis and mRNA splicing halted by the onset of stress;[17 18] and are involved in protein folding and unfolding, assembly and disassembly, and translocation.[19] A further possibility is that stress proteins exert their effect by affording protection against the oxidative stress of reactive oxygen species liberated during post-ischaemic reperfusion: heat shock is accompanied by the induction of the antioxidant catalase within the myocardium.[10] Inhibition of catalase induction has been shown to lessen the protective effect of heat shock.[20]

Do stress proteins protect the heart by other antioxidant mechanisms? A low molecular weight stress protein (SP32) is present in the heart[21] and induced by the reactive oxygen species, hydrogen peroxide.[22] Reactive oxygen species are released early during post-hypoxic reperfusion and have been implicated in myocardial reperfusion injury. SP32 has been identified as haem oxygenase-1,[22] the rate limiting enzyme in the degradation of haem to bilirubin. Bilirubin is a potent scavenger of reactive oxygen species, its efficacy increasing with the decrease in pH[18] associated with ischaemia. Haem oxygenase-1 (SP32) is active only in the presence of oxygen. It is therefore possible that during reperfusion (for example after thrombolysis for myocardial infarction) the induction of haem oxygenase-1 mediated by reactive oxygen species has a protective antioxidant effect.

It may therefore be hypothesised that the heart is protected by the innate ability of the cardiomyocyte to defend itself against hypoxic, oxidant, and haemodynamic stress by the induced expression of a stress protein response. The heart is not unique in this respect: the inflamed joint shows striking similarities.[24] It too is subject to pressure-induced ischaemia and reperfusion events that facilitate the generation of reactive oxygen species and the induction of protective stress proteins.[25] Additionally, the 60 kDa stress protein family has been implicated in inflammatory arthritis,[26,27] inviting speculation that because of the highly conserved nature of stress proteins, molecular mimicry may lead to the development of autoimmunity.[28]

Some fundamental questions remain. Do the stress proteins provide the heart with purely a self defence mechanism or can they also attack (for example in autoimmune conditions such as Dressler's syndrome and lupus carditis)? While research to elucidate the molecular biology of the stress proteins continues, questions about their therapeutic exploitation should be considered. Has this already been achieved during surgery by the hypothermic induction of protective stress proteins during cold cardioplegia and organ transport? Finally, will pharmacological intervention prolong or stimulate the induction of stress proteins, thereby providing a means to protect the myocardium in coronary artery disease?

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1 Ritossa F. A new puffing pattern induced by temperature shock and DNP in *Drosophila. Experentia* 1962;18:571–3.
2 Carper SW, Duffy JJ, Gerner EW. Heat shock proteins in thermotolerance and other cellular processes. *Cancer Res* 1987;47:5249–55.
3 Schlesinger MJ, Ashburner M, Tissieres A, eds. *Heat shock: from bacteria to man*. Cold Spring Harbour Laboratory Press, 1982:1–440.
4 Donati YRA, Slosman DO, Polla BS. Oxidative injury and the heat shock response. *Biochem Pharmacol* 1990;40:2571–7.
5 Knowlton AA, Brecher P, Apstein CS. Rapid expression of heat shock proteins in the rabbit after brief cardiac ischaemia. *J Clin Invest* 1991;87:139–47.
6 Reimer KA, Murry CE, Jenning RB. Cardiac adaptation to ischaemia. *Circulation* 1990;82:2266–8.
7 Deutsch E, Berger M, Kessmaul WG, Hirschfield JW, Laskey WK. Adaptation to ischaemia during percutaneous transluminal coronary angioplasty. *Circulation* 1990;82:2044–51.
8 Currie RW, Ross BM, Davies TA. Induction of the heat shock response in rats modulates heart rate, creatine kinase and protein synthesis after a subsequent hyperthermic treatment. *Cardiovasc Res* 1990;24:87–93.
9 Stress proteins and myocardial protection. *Lancet* 1991;337:271–2.
10 Currie RW, Karmazyn M, Kloc M, Mailer K. Heat shock response is associated with enhanced postischemic ventricular recovery. *Circulation Res* 1988;63:543–9.
11 Yellon DM, Pasini E, Ferrari R, Downey JM, Latchman DS. Whole body heat shock protects the isolated perfused rabbit heart [abstract]. *Circulation* 1990;82(**suppl 111**):1839.
12 Thornton JD, Sriplin S, Liu GS, Swafford A, Stanley AWH, van Winkle DM, *et al.* Inhibition of protein synthesis does not block myocardial protection afforded by preconditioning. *Am J Physiol* 1990; 259:H1822–5.
13 Hightower LE, White FP. Preferential synthesis of rat heat shock and glucose-regulated proteins in stressed cardiovascular cells. In: Schlesinger MJ, Ashburner M, Tissieres A, eds. *Heat shock: from bacteria to man*. Cold Spring Harbour Laboratory Press, 1982:369–77.
14 Ellis RJ, Hemmingsen SM. Molecular chaperons: proteins essential for the biogenesis of some macromolecular structures. *Trends Biochem Sci* 1989; 14:339–42.
15 Delcayre C, Samuel JL, Marrotte F, Best-Belpomme M, Mercadier JJ, Rappaport L. Synthesis of stress proteins in rat cardiac myocytes 2–4 days after imposition of haemodynamic overload. *J Clin Invest* 1988;82:460–8.
16 Winrow VR, McLean L, Morris CJ, Blake DR. The heat shock protein response and its role in inflammatory disease. *Ann Rheum Dis* 1990;49: 128–32.
17 Welch WJ, Suhan JP. Morphological study of the mammalian stress response: characterisation of changes in cytoplasmic organelles, cytoskeleton and nucleoli, and appearance of internuclear actin filaments in rat fibroblasts after heat shock treatment. *J Cell Biol* 1985;101:1198–211.
18 Yost HJ, Lindquist S. RNA splicing is interrupted by heat shock and is rescued by heat shock protein synthesis. *Cell* 1986;45:185–93.
19 Lindquist S, Craig EA. The heat shock proteins. *Ann Rev Genet* 1988; 22:631–7.
20 Karmazyn M, Mailer K, Currie RW. Acquisition and decay of heat shock-enhanced postischemic ventricular recovery. *Am J Physiol* 1990;259: H424–31.
21 Schuman J, Przybyla A. Expression of the 31 kDa stress protein in rat myoblasts and hepatocytes. *DNA* 1988;7(7):475–82.
22 Keyse SM, Tyrell RM. Heme oxygenase is the major 32 kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide and sodium arsenite. *Proc Natl Acad Sci USA* 1989;86:99–103.
23 Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. *Science* 1987; 235:1043–6.
24 Winrow VR, Blake DR. Stress proteins, hearts and joints. *Lancet* 1991;337: 614–5.
25 Allen RE, Blake DR, Nazhat NB, Jones P. Superoxide generation by inflamed human synovium after hypoxia. *Lancet* 1989;ii:282–32.
26 Winrow VR, Mojdehi G, Mapp PI, Rampton DS, Blake DR. Immunohistological localisation of stress proteins in inflammatory tissue. In: Burdon R, Rice-Evans C, Blake DR, Winrow V, eds. *Stress Proteins in Inflammation*. London: Richlieu Press, 1990;137:237–51.
27 van Eden W, Thole JER, van der Zee R, Noordzij A, van Embden JDA, Hensen EJ, *et al.* Cloning of the mycobacterial epitope recognised by T lympohocytes in adjuvant arthritis. *Nature* 1988;331:171–3.
28 Tsoulfa G, Rook GAW, van Embden JDA, Young DB, Mehlert A, Isenberg DA, Hay FC, Lydyard PM. Raised serum IgA and IgG antibodies to mycobacterial antigens in rheumatoid arthritis. *Ann Rheum Dis* 1989;48:118–23.

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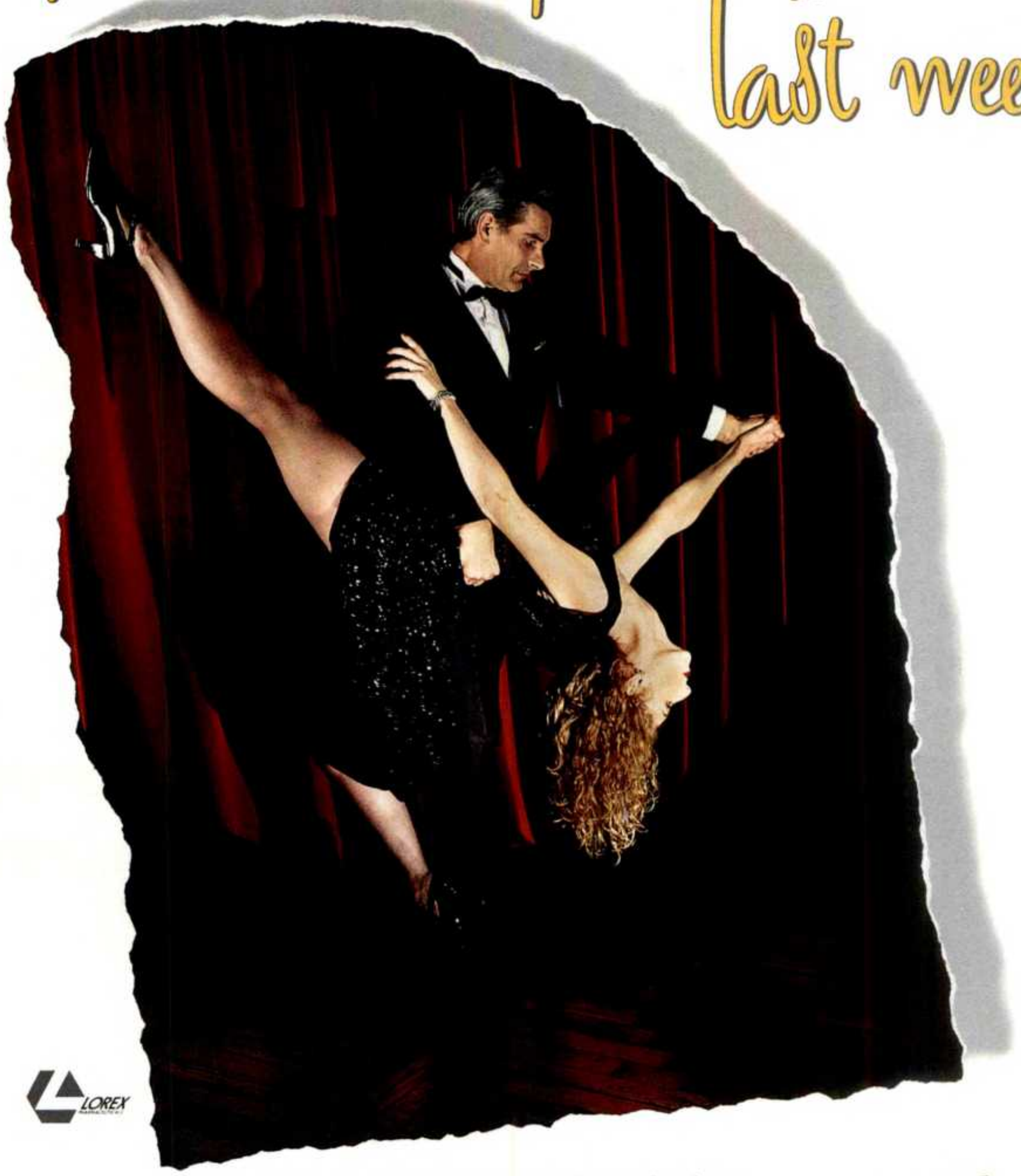

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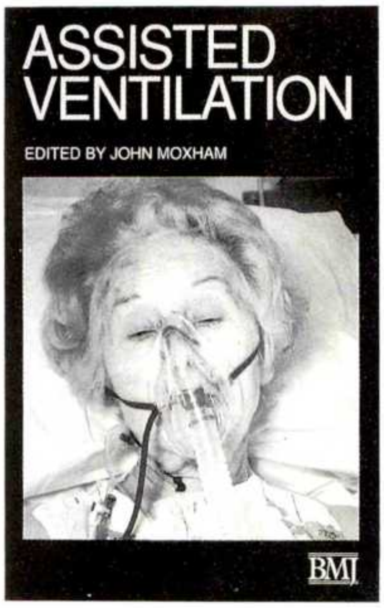

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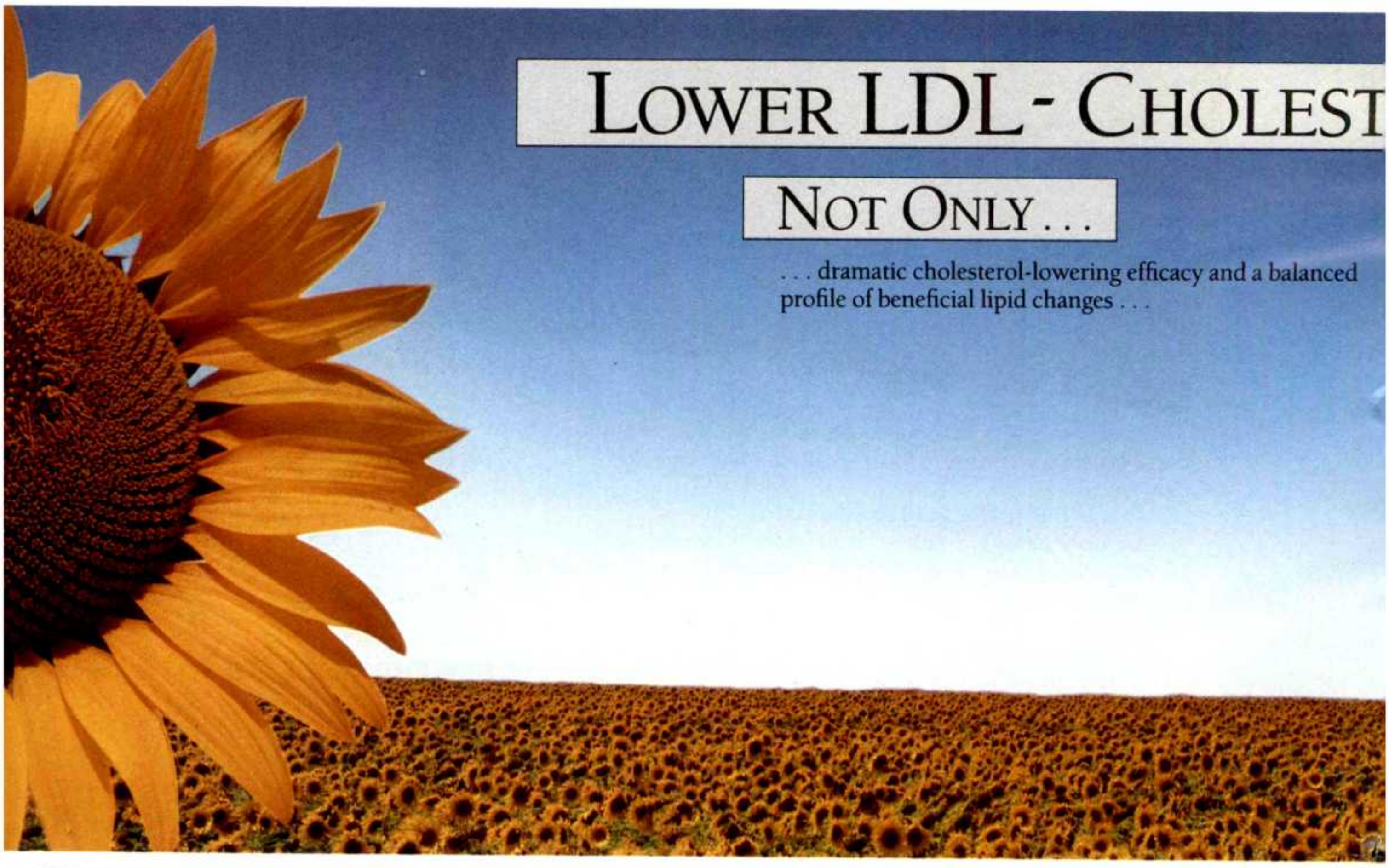
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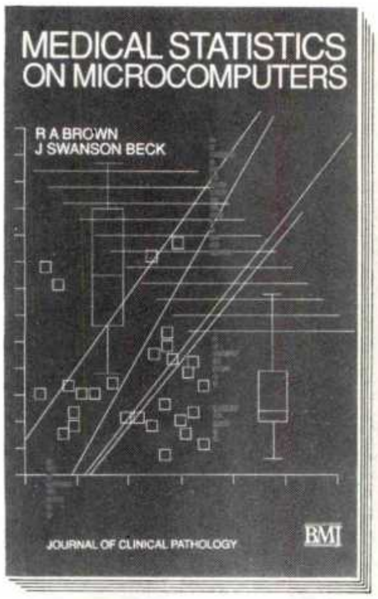
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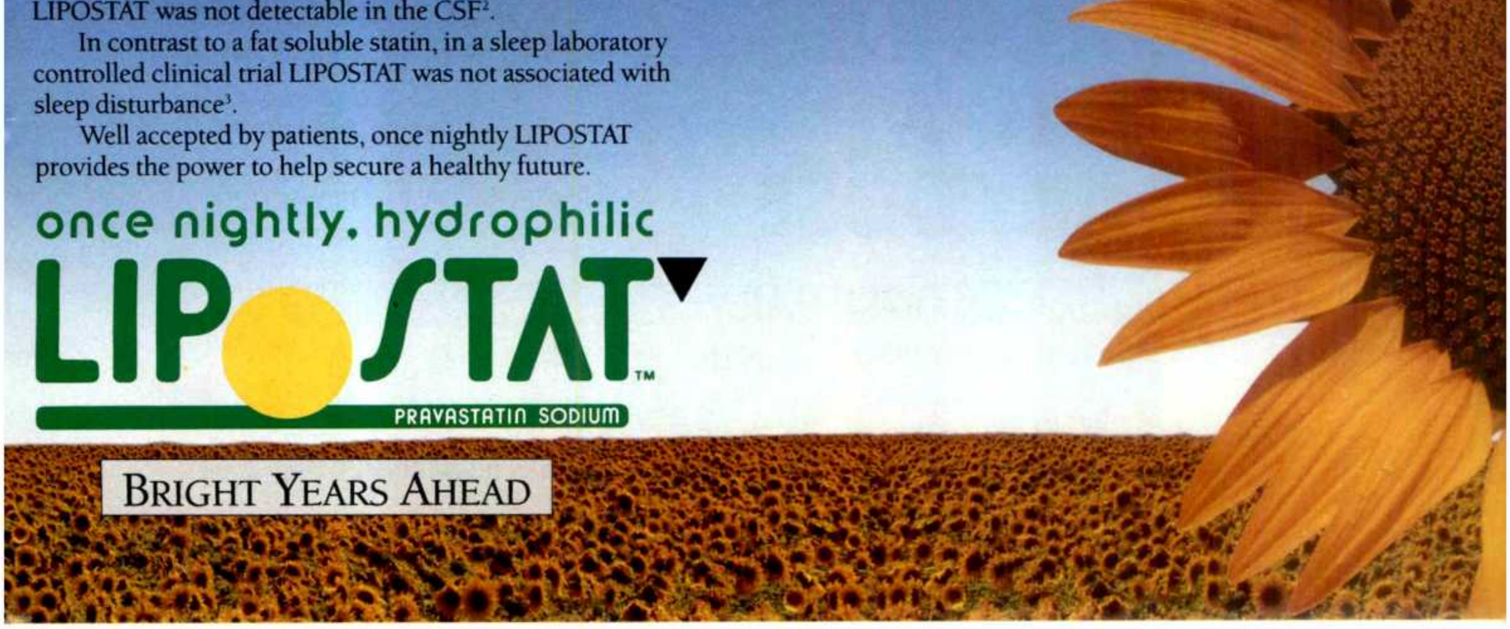

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References
1. Data on file. In trials LIPOSTAT demonstrates an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).
2. Botti RE et al. Clin Neuropharm 1991; **14 (3)**: 256-261.
3. Bixler EO. Round Table Discussion, Lipid Management, Pravastatin and the Differential Pharmacology of HMG-CoA Reductase Inhibitors. Proceedings of a panel discussion held in London on 5th July 1989. Royal Society of Medicine Services Round Table Series 1990; 16: 32-40.

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REVIEW

Antiphospholipid antibodies and cardiovascular disease

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Vascular inflammation is a common feature of autoimmune diseases including systemic lupus erythematosus and the primary vasculitides (for example, polyarteritis nodosa, Wegener's granulomatosus, and Takayasu's arteritis). This inflammation is characterised by destruction of the vessel wall; perivascular infiltration of neutrophils, monocytes, and lymphocytes; and deposition of immunoglobulins and complement proteins.[1 2] A novel type of autoimmune vascular damage has been characterised during the past few years associated with the presence of antiphospholipid antibodies. The predominant manifestation is vascular thrombosis in the absence of other markers of tissue inflammation.

Three techniques are commonly used in clinical practice to identify antiphospholipid antibodies. In order of increasing sensitivity these are the VDRL (Venereal Diseases Reference Laboratory), lupus anticoagulant, and anticardiolipin antibody (ACA) assays. Cardiolipin is the most usual antigen used in antiphospholipid antibody assays and was chosen for historical reasons because it is a constituent of the VDRL reagent. However assays for antibodies to other negatively charged phospholipids, such as phosphatidylserine and phosphatidic acid seem to be equally sensitive and much work is needed to define the best method of identifying these antibodies in clinical practice.

Antiphospholipid antibodies are found in two main clinical settings: (*a*) after chronic infection—for example, syphilis, malaria, leprosy—and (*b*) associated with autoimmunity. Only in autoimmune diseases do these antibodies correlate with thrombosis. The VDRL and anticardiolipin antibody assays do not distinguish between antiphospholipid antibodies associated with infection or autoimmunity—therefore interpretation of the relevance of a positive result from these assays is dependent on the clinical circumstances. In contrast, the lupus anticoagulant is more specifically found in association with autoimmune disease including the "primary antiphospholipid syndrome". However, it may also be found after treatment with certain drugs, such as chlorpromazine, and its clinical significance in this context is not certain. The test for lupus anticoagulant is technically more difficult and less sensitive than the newly established methods for detecting anticardiolipin antibodies.

Four questions about the association of these autoantibodies with cardiovascular disease will be considered here: (*a*) what is the nature of their association with thrombosis, valve lesions, and pulmonary hypertension; (*b*) is there any true association with coronary artery disease; (*c*) are the antibodies causally related to disease; and (*d*) what is the best treatment? The other significant clinical and haematological associations with these autoantibodies (recurrent spontaneous abortions, haemolytic anaemia combined with thrombocytopenia, and chorea gravidarum) fall outside the scope of this review and have been reviewed elsewhere.[3 4]

Thrombosis

Thrombosis of the veins and arteries is the commonest clinical feature associated with the presence of antiphospholipid antibodies. These thrombotic events are often repeated and almost every portion of the circulation can be affected. Indications for assay of anticardiolipin antibodies include recurrent deep venous thromboses, early onset cerebrovascular disease (which may be associated with cognitive impairment and progression to multi-infarct dementia), and unexplained thrombosis in other circulations. The table shows the list of thrombotic events anecdotally associated with the presence of anticardiolipin antibodies. The eponymous Sneddon's syndrome, comprising livedo reticularis and cerebrovascular disease, is often associated with these autoantibodies.[5]

Valve disease

Libman and Sachs reported in 1924 a "hitherto undescribed form of valvular and mural endocarditis" in patients with systemic lupus erythematosus.[6] There is now good evidence for an association of this form of endocarditis with the presence of antiphospholipid antibodies. In patients with systemic lupus erythematosus Galve and colleagues in 1989 found anticardiolipin antibodies in eight out of nine patients with valve lesions and seven out of 16 patients without.[7] This finding has been confirmed in a recent prospective analysis in which high titres of antiphospholipid antibodies (>5 SDs above the normal mean) were detected in 50 of 93 patients with systemic lupus erythematosus.[8] Thirty nine of the patients with raised titres of anticardiolipin antibody were found to have at least one cardiac abnormality. Valve lesions predominantly affecting the mitral valve were present in 20 (vegetations in eight and diffuse valve thickening in 12). Pericardial effusion was present in 15 patients and four patients had evidence of myocardial dysfunction. In this study the overall sensitivity and specificity of high titres of anticardiolipin antibodies in predicting cardiac abnormalities in systemic lupus erythematosus was 78% and 74% respectively. In the same study eight of 12 patients with high titres of antiphospholipid antibodies who did not fulfil the American Rheumatism Association criteria for systemic lupus erythematosus also had cardiac abnormalities: four had mitral valve vegetations, three had diffuse thickening of the mitral valve, and one had severe aortic regurgitation. Others have confirmed the association between antiphospholipid antibodies and valvar heart disease in similar groups of patients.[9-12] There is an appreciable chance of ascertainment artefact resulting in the collection of biased data in such studies—that is, obstetricians are more likely to see a high prevalence of recurrent abortions in patients with antiphospholipid antibodies and it is not surprising that cardiologists also report that cardiac disease is common.

Vascular associations of antiphospholipid antibodies

Arterial disease
- thrombosis of large arteries leading to: stroke, splenic infarction, mesenteric infarction etc.
- multi-infarct dementia
- marrow necrosis
- retinal artery disease
- deafness and vestibular failure
- adrenal infarction
- skin necrosis
- coronary thrombosis (see text)
- pulmonary hypertension

Venous disease
- recurrent deep venous thromboses with or without emboli
- Budd-Chiari syndrome

Placenta
- thrombosis of placental vessels

Pulmonary hypertension

Primary pulmonary hypertension was found in up to 14% of patients with systemic lupus erythematosus.[13 14] In an uncontrolled study of 24 patients with autoimmune disease and pulmonary hypertension (22 systemic lupus erythematosus, one primary antiphospholipid antibody syndrome, one lupus/systemic sclerosis overlap) 21 patients had primary pulmonary hypertension with no evidence of thromboembolism and antiphospholipid antibodies were detected in 68%, compared with a background frequency in systemic lupus erythematosus of 30–40%.[13 14] Further work is needed to establish whether this association is genuine.

Is coronary artery disease significantly associated with antiphospholipid antibodies?

Given that coronary artery disease is so common it would be surprising if there was a marked association of this condition with antiphospholipid antibodies. It was therefore remarkable when a prevalence of anticardiolipin antibodies of 21% was reported among 62 young (<45 years) survivors of myocardial infarction without other evidence of autoimmune disease.[15] During a five year follow up cardiovascular events (including stroke, lower limb occlusion, new myocardial infarction, and pulmonary embolism) were more common in eight out of 13 patients with raised titres of anticardiolipin antibody. No clinical features separated the groups of patients with or without anticardiolipin antibodies at the time of initial presentation with myocardial infarction. This study raises two questions: (*a*) which came first—the coronary artery disease or the anticardiolipin antibodies and (*b*) what relation, if any, did the subsequent vascular disease have to the autoantibody? Two other groups have also reported raised titres of anticardiolipin antibodies in cohorts of patients with coronary artery disease: (*a*) anticardiolipin antibody titres were raised in patients with angina and/or infarction compared with groups of patients with tuberculosis or rheumatoid arthritis[16] and (*b*) there was a significant correlation between anticardiolipin titres (measured at the time of coronary artery bypass surgery) and the incidence of late graft occlusions.[17]

It is important to appreciate that the cut off point for "positive" results in each of these studies was 2 SDs above the normal mean—that is, a value that includes 5% of a normal population. This cut off value is much lower than the value of 5 SDs usually chosen in analyses of patients with systemic autoimmunity.

Other surveys[18 19] of consecutive patients with coronary artery disease have not confirmed an association with anticardiolipin antibodies and the pathogenic significance of the low titres of these antibodies measured by some workers in these patients remains doubtful.

What is the prevalence of coronary artery disease among patients with autoimmunity and antiphospholipid antibodies? Myocardial infarction was identified in 13 (six systemic lupus erythematosus, three lupus like disease, and four primary antiphospholipid syndrome) of 300 patients with high titres of antiphospholipid antibodies.[20] This low prevalence of 4% myocardial infarction among patients with very high titres of anticardiolipin antibodies casts further doubt on the pathogenic significance of low titres of antibodies in some series of patients with coronary artery disease in the absence of other evidence of autoimmunity.

Pathogenesis

The data reviewed above strongly support the existence of genuine epidemiological associations of a subset of antiphospholipid antibodies with thrombotic vascular disease and with endocarditis, though the strength of these associations requires further clarification. The target of these autoantibodies in vivo has not been identified. Negatively charged phospholipids are widely distributed in cell membranes, but they are mainly located on the inner lamella of the cell membrane and in this location are not accessible to autoantibodies.[21] Recent work has suggested that antigenicity in vitro of antiphospholipid antibodies depends on the interaction of the phospholipid with a protein cofactor β_2 glycoprotein I (apolipoprotein H).[22] It is unknown whether a cofactor is involved in vivo.

The in vitro and in vivo effects of antiphospholipid antibodies are paradoxical. In vitro the lupus anticoagulant prolongs the partial thromboplastin time by inhibiting the binding of the factor X and prothrombinase complexes to anionic phospholipid substrate.[23] In contrast, these antibodies are associated with thrombosis in vivo and several hypotheses have been proposed to explain this: (*a*) activation of platelets; (*b*) endothelial activation rendering the antibody procoagulant (inhibition of prostacyclin generation, inhibition of thrombomodulin generation of active protein C); (*c*) inhibition of fibrinolysis by interference with protein C and S function; (*d*) impaired prekallikrein action; and (*e*) inhibition of antithrombin III (reviewed in [24]). None of the mechanisms has been convincingly proven to operate in vivo. It is noteworthy that inherited deficiencies of proteins C, S, and antithrombin III are each associated with recurrent venous, but not arterial, thromboses.

Treatment

It is disappointing that the treatment of patients with antiphospholipid antibodies has not developed beyond the empirical stage and no formal clinical trials have been published. It is common practice to prescribe long-term anticoagulation with warfarin for patients with venous thrombosis and antiphospholipid antibodies, because there is some evidence that there is a high risk of recurrent thrombosis when such treatment is stopped.[25] Significant valve lesions should be sought so that patients can be advised about antibiotic prophylaxis.

All other management issues are uncertain. Arterial disease, especially cerebrovascular, poses particular difficulties because there is good evidence of insidious progression in some patients.[26] Warfarin combined with low dose aspirin is a reasonable empirical treatment but there are no data showing effectiveness or ineffectiveness. The role of immunosuppression is even more uncertain—removing the antibodies is fine in principle but in practice requires the administration of large doses of steroids and cytotoxic agents. Corticosteroids are widely prescribed to patients with antiphospholipid antibodies, but there are no controlled data and this practice is not based on logical premises. In other autoimmune diseases such as systemic lupus erythematosus steroids are potent anti-inflammatory agents. There is no evidence that classic inflammatory mechanisms are involved in the pathogenesis of the vascular associations of the antiphospholipid syndrome. For this reason we usually restrict steroids and cytotoxic drugs to patients with co-existing systemic lupus erythematosus or related diseases with other clinical manifestations of inflammation.

Conclusion

The delineation of the clinical syndrome associated with antiphospholipid antibodies has defined new challenges for clinicians and scientists interested in vascular biology. During the first major rush of enthusiasm it is likely that most of the important clinical correlates of the importance of these antibodies have been discovered. The important questions that now remain to be answered are: (*a*) what is the relevant antibody specificity and how should it be measured, (*b*) if the pathogenesis of thrombosis is mediated by the antibody, what is the mechanism, (*c*) what is the prevalence of the different clinical features of the syndrome in unselected individuals with antiphospholipid antibodies and what is the scale of the problem overall (that is, to what extent do "pathogenic" antiphospholipid antibodies contribute to thrombosis in unselected cohorts of patients), and (*d*) what is the best treatment? There are still more questions than answers.

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1 Beynon HLC, Neild GH, Pusey CD, Walport MJ. Vasculitis and endothelium. In: Warren JB, ed. *The endothelium*. New York: Wiley-Liss, 1990:209–27.
2 Fauci AS. The spectrum of vasculitis. Clinical, pathogenic, immunogenic, and theraputic considerations. *Ann Intern Med* 1978;89:660–76.
3 Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RHWM, Machin SJ, Barquinero J, *et al*. The "primary antiphospholipid syndrome": Major clinical and serological features. *Medicine (Baltimore)* 1989;68:366–74.
4 Mackworth-Young CG, Loizou S, Walport MJ. Antiphospholipid antibodies and disease. *Q J Med* 1989;72:767–77.
5 Englert H, Derue G, Hughes GRV. Neurology and the lupus anticoagulant. *Eur Neurol* 1985;24:422–5.
6 Libman E, Sachs B. A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med* 1924;33:701–37.
7 Galve E, Ordi J, Candella-Riera J, Permanyer-Miralda G, Vilardell M, Soler-Soler J. Valvular heart disease in systemic lupus erythematosus [letter]. *N Engl J Med* 1989; 320:740–1.
8 Nihoyannopoulos P, Gomez PM, Joshi J, Loizou S, Walport MJ, Oakley CM. Cardiac abnormalities in systemic lupus erythematosus. *Circulation* 1990;82:369–75.
9 Chartash EK, Lans DM, Paget SA, Qamar T, Lockshin MD. Aortic insufficiency and mitral regurgitation in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am J Med* 1989;86:407–12.
10 Ford SE, Charrette EJP, Knight J, Pym J, Ford P. A possible role for antiphospholipid antibodies in acquired cardiac valve deformity. *J Rheumatol* 1990;17:1499–503.
11 Khamashta MA, Cervera R, Asherson RA, Font J, Gil A, Coltart DJ, Vazquez JJ, *et al*. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. *Lancet* 1990;335:1541–4.
12 Leung WH, Wong KL, Lau CH, Wong CK, Liu HW. Association between antiphospholipid antibodies and cardiac abnormalities in patients with systemic lupus erythematosus. *Am J Med* 1990;89:411–9.
13 Asherson RA, Hingebottam TW, Xuan ATD, Khamashta MA, Hughes GRV. Pulmonary hypertension in a Lupus clinic; Experience with twenty four patients. *J Rheumatol* 1990;17:1292–8.
14 Asherson RA, Oakley CM. Pulmonary hypertension in SLE. *J Rheumatol* 1986;13:1–5.
15 Hamsten A, Norberg R, Bjorkholm M, de-Faire U, Holm G. Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet* 1986;18:113–6.
16 Klemp P, Cooper RC, Strauss FJ, Jordaans ER, Przybojewski JZ, Nel N. Anticardiolipin antibodies in ischaemic heart disease. *Clin Exp Immunol* 1988;74:254–7.
17 Morton KE, Gavaghan TP, Krilis SA, Daggard GE, Baron DW, Hickie JB, *et al*. Coronary artery bypass graft failure—an autoimmune phenomenon? *Lancet* 1986; ii:1353–7.
18 De Caterina R, d'Ascanio A, Mazzone A, Gazzetti P, Bernini W, Neri R, *et al*. Prevalence of anticardiolipin antibodies in coronary artery disease. *Am J Cardiol* 1990;65: 922–4.
19 Eber B, Kronberger-Schaffer E, Brussee H, Klima G,

Obernosterer A. Anticardiolipin antibodies are no marker for survived myocardial infarction. *Klin Wochenschr* 1990;68:594–6.

20 Asherson RA, Khamashta MA, Baguely E, Oakley CM, Rowell NR, Hughes GRV. Myocardial infarction and antiphospholipid antibodies in SLE and related disorders. *Q J Med* 1989;73:1103–15.

21 Khamashta MA, Harris EN, Gharavi AE, Derue G, Gil A, Vazqueez JJ, *et al.* Immune mediated mechanism for thrombosis: antiphospholipid antibody binding to platelet membranes. *Ann Rheum Dis* 1988;47:849–54.

22 Galli M, Comfurius P, Maassen C, Hemker HC, De Baets MH, Van Breda-Vriesman PJC, *et al.* Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet* 1990;335:1544–7.

23 Pengo V, Thiagarajan P, Shapiro SS, Heire MJ. Immunological specificity and mechanism of action of IgG lupus anticoagulant. *Blood* 1987;70:69–76.

24 Mackworth-Young C. Antiphospholipid antibodies: more than just a disease marker? *Immunol Today* 1990;11:60–5.

25 Asherson RA, Harris EN, Gharavi AE, Hughes GRV. Anticardiolipin antibody, recurrent thrombosis and warfarin withdrawal. *Ann Rheum Dis* 1985;44:823–5.

26 Asherson RA, Mercy D, Philips G, Sheehan S, Gharavi AE, Harris EN, *et al.* Recurrent stroke and multiinfarct dementia in systemic lupus erythematosus associated with antiphospholipid antibodies. *Ann Rheum Dis* 1987;46:605–11.

VIEWS FROM THE PAST *George Dock*

There is no new thing under the sun.

Ecclesiastes 1.9

In this era when angiography, angioscopy, and pathology have concentrated on the importance of plaque disruption in causing coronary thrombosis it is salutatory to discover astute observations made in the last century.

George Dock in 1896 made observations that have a remarkably modern ring. . .

Why then did pathologists subsequently deny the importance of thrombosis? Perhaps because they had become remote from the clinical aspects of disease. That cannot be said of George Dock who was successively Professor of Pathology in Galveston, Professor of the Theory and Practise of Medicine, University of Michigan, and Professor of Medicine in St Louis.

M J DAVIES

> A negro drayman, of fifty, a man of unusually powerful physique, with a history of perfect health, was seized in the night with pain in the heart-region and a sense of suffocation. He was seen by Dr H A West, who found no special symptoms other than those mentioned. Morphine temporarily relieved the pain, but in about two hours after the onset the patient suddenly died. I made an autopsy six hours after death, and, finding no marked evidence of disease in any other organ, took the heart unopened to my laboratory for careful examination. This was made by cutting the organ in slices, parallel to the auriculo-ventricular septum, and examining the vessels in each slice separately. . . . The branches of the aorta were all free from atheroma except the coronaries. The latter were affected in various degrees in their whole extent, being calcified, partially occluded or dilated. In the descending branch of the left, just below its origin, was a ruptured atheromatous abscess, eight mm long, extending two-thirds around the dilated artery. The edges were overhanging, the flow uneven and ragged, presenting all the appearances of a recent rupture. This proved to be the case. On opening up the sections of the branches below the rupture they were found to contain a little blood with characteristic atheromatous material, such as cholesterin plates, blood pigment in crystals and masses, larger cells with highly refracting granules and amorphous and granular debris. The left lateral branch of the artery just below the rupture was obstructed by an atheromatous nodule in its wall, but all the other branches contained debris as far as they could be traced.
>
> George Dock. Notes on the coronary arteries. In: Mauer AK, Mauer EF. *George Dock, MD: a bibliography of his writings*. 2nd ed. Los Angeles: Barlow Society for the History of Medicine/Friends of the Library of the Los Angeles County Medical Association, 1991.

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, 63, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

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VIEWPOINT

Is VVI pacing outmoded?

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Pacing is a common clinical procedure. The permanent implant rate in the United Kingdom is lower than in other Western countries. The last World Survey[1] showed a new implant rate of 148 per million population per year (8346 systems) in the United Kingdom. This compares with 421 in Germany, 413 in France, 359 in the United States, and 175 in Spain. In the United Kingdom, the pacing mode was simple constant rate ventricular inhibited (VVI)[2] in about 78%, despite the widespread availability of more physiological systems. This proportion has not changed significantly in more recent years. It is our view that the simple VVI mode is not appropriate in 1992 and that almost every patient would be better served by an alternative mode, even though these other modes may take more time to implant and follow-up, may cost more, and require some expertise, which may easily be acquired.

Indications for permanent pacing

The major indications for pacing for bradycardia are symptom relief and the improvement of prognosis. Symptoms of bradycardias include syncope (Adams-Stokes' attacks), lesser degrees of disturbed consciousness, breathlessness, fatigue, and chest pain. Depending on the underlying pathology, other symptoms may be secondary to associated abnormal tachycardias or emboli. The prognosis is influenced by the underlying pathology. The major pathologies are sinoatrial disease (31% of United Kingdom implants) and atrioventricular conduction abnormalities (54%) as well as carotid sinus hypersensitivity. These entities may occur alone or in combination. Pacing may also be indicated for the termination of reentrant tachycardias but this is an uncommon indication and is beyond the scope of this article.

Pacing modes

In 1958 the first permanent pacemaker was implanted into a human.[3] This was an epicardial, ventricular fixed rate device. Since then pacemaker complexity has increased until endocardial pacing and sensing of the right atrium, right ventricle, or both are possible with programmable devices that can vary the pacing rate according to the patient's needs.

Simple ventricular demand pacemakers commit the patient to a constant pacing rate and are unresponsive to fluctuating metabolic needs. Atrioventricular synchrony is lost and retrograde atrioventricular conduction may occur producing unpleasant symptoms and deleterious haemodynamic effects (pacemaker syndrome).[4] Symptoms of the pacemaker syndrome include breathlessness, weakness, dizziness, presyncope, pulsations in the neck and palpitation. Heldman *et al* randomised 40 patients blindly to VVI or dual chamber pacing in a crossover study.[5] Pacemaker syndrome was recognised in 83% of patients in the VVI mode and was moderate or severe in 65% (intolerable in 42%). Atrial pacing alone may be useful in some patients with sinoatrial disease.

To overcome problems associated with a constant pacing rate, more sophisticated pacemakers have been developed. One solution has been to control the pacing rate according to one of a multitude of physiological variables (rate responsive pacing). These include variables such as the QT interval,[6] respiratory rate,[7] minute ventilation,[8] mixed venous temperature,[9] or oxygen saturation,[10] which reflect metabolic needs. Other sensors simply respond to varying levels of activity by detecting motion in different ways.[11 12] All these systems have been shown to be clinically practical and useful, and implantation is usually identical to a standard single chamber system. There are problems with all of these systems, however; some of them may be specifically sensor related.[13–15] Furthermore, patients with ventricular demand systems (VVIR) will also lose atrioventricular synchrony and may be subject to the pacemaker syndrome. In addition, some sensors are not ideal for atrial rate-responsive demand pacing (AAIR).

Another method of obtaining rate response is to sense the natural atrial rate. This requires a dual chamber system. Originally these systems could neither pace the atrium nor sense the ventricle (VAT mode). Then ventricular sensing was achieved (VDD mode), and now most dual chamber pacemakers are capable of operating in the "universal" DDD mode, which allows atrial synchronous ventricular pacing with additional demand atrial pacing and ventricular sensing. A more recent development has been the DDI mode which allows atrioventricular sequential pacing at a constant rate with both atrial and ventricular sensing but where ventricular pacing is not triggered by atrial sensing. The DVI mode, which has been superseded by DDI, was similar but without atrial sensing.

Conventional dual chamber pacemakers overcome many problems by providing rate response, maintaining atrioventricular synchrony, and preventing the pacemaker syndrome. Their value is limited when there is chronotropic incompetence or if there are persistent atrial arrhythmias. Problems specific to dual chamber pacemakers are related to implantation and to the increased complexity of the hardware. Two pacing leads are generally required, although single pass leads have occasionally been used. Refinements such as the development of thin bipolar leads with various fixation mechanisms have circumvented problems related to both implantation and atrial sensing so that most centres find little additional difficulty with dual chamber compared with single chamber implants. Joseph *et al*,[16] in a district general hospital, had a long-term success rate of 98% using modern atrial leads. Pacemaker mediated reentrant or "endless loop" tachycardia is a problem exclusive to dual chamber pacemakers.[17] It occurs in some patients with retrograde conduction (from ventricle to atrium) through sensing of retrograde atrial activation, and is often at the upper rate limit of the pacemaker. However, modern pacemaker design has minimised this problem.

To cope with patients with chronotropic incompetence, some dual chamber pacemakers are now available with a non-atrial sensor thus offering, for example, DDDR or DDIR pacing. These pacemakers also allow selection of the ventricular rate responsive mode if, for example, atrial fibrillation develops in a patient already being paced for atrioventricular block.

Choice of pacemaker

SINOATRIAL DISEASE

Special considerations when pacing patients with sinoatrial disease include improving the overall prognosis, the prevention of atrial tachycardias, overcoming an increased risk of thromboembolic events, and the state of atrioventricular conduction (anterograde and retrograde). There are few data on overall mortality in this disorder, although Shaw *et al* described a survival rate similar to a matched control population.[18] However, some of their patients had only mild sinoatrial abnormalities. Pacing did not seem to alter prognosis in this study, but most of the patients were paced only from the ventricle.

Rosenqvist *et al* showed that in patients free from atrial fibrillation at the time of implant, 47% of those paced from the ventricle (VVI) developed persistent atrial fibrillation compared with 6·7% ($p < 0{\cdot}0005$) paced with atrial inhibited pacemakers (AAI) over a four year follow up.[19] The VVI group had a higher incidence of congestive heart failure (37%) than the AAI group (15%, $p < 0{\cdot}005$), and a higher mortality (23% compared with 8%, $p < 0{\cdot}05$). Several other studies have also shown the value of pacing the atrium in preventing atrial fibrillation.[20-22] The risk of systemic embolism probably influences the prognosis, and this is in turn linked to the development of supraventricular tachycardias, especially atrial fibrillation. Sutton and Kenny pooled data from several studies (853 patients) and showed a 1·6% incidence of systemic emboli in AAI paced patients compared with 13% in VVI paced patients ($p < 0{\cdot}001$).[23] Many patients with sinus node disease have intact retrograde atrioventricular conduction and are thus at risk from the pacemaker syndrome if paced from the ventricle alone.[24] For all of these reasons, pacing systems for patients with sinus node disease should at least incorporate an atrial lead.

For single chamber pacing, the AAI mode may be used. If there is significant chronotropic incompetence, a rate responsive system (AAIR) can be chosen,[25] although this imposes increased stress on atrioventricular conduction. Although many sensors are suitable for AAIR pacing, the QT interval is an obvious exception; atrial temperature based sensor systems can be unreliable, and even with activity based systems there have been problems.

AAI or AAIR pacing is inappropriate for patients with sinoatrial disease together with impaired atrioventricular conduction at the time of diagnosis. In addition, some of the patients with normal conduction at the time of implant may develop impairment of atrioventricular conduction with time. Rosenqvist *et al* documented the development of high grade atrioventricular block in 4 of 89 patients (4·5%) paced from the atrium over a 4 year period.[19] Rosenqvist and Obel surveyed published reports and found 28 studies, relating to 1878 patients followed for a median period of three years.[26] The median prevalence of development of significant atrioventricular block was 2·1%, an annual incidence of 0·6%. Thus there is a risk of developing significant atrioventricular block with time, but the risk is low.

The development of chronic atrial fibrillation will render atrial pacemakers ineffective, but many patients will have adequate ventricular response rates. Some suggest that dual chamber pacing should be the rule in patients with sinoatrial disorders because of these limitations,[23] but this remains controversial.

If dual chamber pacing is chosen in patients with sinoatrial disease, care must be taken to select the correct mode. The high incidence of retrograde conduction in these patients means that there is often an ideal substrate for pacemaker mediated "endless loop" tachycardias. These may complicate DDD pacing so that DDI pacing is often preferred. The advent of dual chamber, sensor responsive pacemakers has allowed DDDR or DDIR pacing in these patients, with DDIR being ideal for many.

ATRIOVENTRICULAR BLOCK

The prognosis of patients with atrioventricular block is radically improved by even the simplest form of ventricular pacing.[27] In certain cases this can be further improved by more sophisticated pacing, but in almost all cases the quality of life can be enhanced by the correct choice of pacemaker.[28-30]

The principal determinant of cardiac output in paced patients is the heart rate.[31] Patients with rate responsive pacemakers perform better during exercise than those with simple VVI devices, whether or not the increase in rate is achieved synchronously (VAT, VDD, or DDD pacemakers)[28 30 32] or asynchronously (VVIR pacemakers).[33 34] Pacemakers that provide only atrioventricular synchrony without atrial tracking (DVI or DDI modes) provide only a small increase in exercise performance.

As comparable improvement is obtained with VVIR and dual chamber pacing, what governs the choice between them? Single chamber VVIR pacing is simple to implement and is the method of choice when chronic atrial arrhythmias are present, when an atrial lead would be ineffective. Dual chamber systems avoid the pacemaker syndrome, which is common in VVI or VVIR modes, and if sinus node function is normal, use the best possible sensor—atrial rate. However, "endless loop" tachycardias are a very occasional nuisance. Initial programming is also simpler with DDD systems, because VVIR pacemakers require the correct relation between the sensor and exercise performance to be ascertained. Overall, the prognosis of patients with atrioventricular block has not been shown to be significantly improved by chosing dual chamber rather than ventricular pacing.[35] However, Alpert *et al* found improved one, three and five year survival in a subset of patients with congestive heart failure treated with DDD compared with VVI pacing.[35] Kenny *et al* also found particular benefit could be gained from treating patients with angina with dual chamber devices rather than ventricular systems, provided the upper rate was limited to 110 beats per minute.[36] Rate responsive dual chamber pacemakers offer complete flexibility for patients with atrioventricular block who have additional chronotropic incompetence.

CAROTID SINUS SYNDROME

In these patients, sinus bradycardia or arrest is common, as is atrioventricular block. These aspects can easily be treated with pacing. The vasodepressor element is present to a greater or lesser degree in most patients, and may be exacerbated by ventricular pacing.[37] Intact retrograde conduction is common (80%),[37] and therefore the pacemaker syndrome is likely with ventricular pacing. Hysteresis (a feature where the pacemaker has a faster pacing rate than sensing rate) may reduce but not abolish these problems. Dual chamber pacing is preferred for these patients. Because the atrial rate response to exercise is usually normal and retrograde conduction is common, the DDI mode is usually recommended.

Recommended pacing modes (codes are defined in the text)

Diagnosis	*Optimal mode*
Sino-atrial disease	AAI/AAIR*
Atrioventricular block	DDD/DDDR*
Sinoatrial disease + persistent atrioventricular block	DDD/DDDR*
Sinoatrial disease + occasional or threatened atrioventricular block	DDI/DDIR*
Atrioventricular block + chronic atrial arrhythmias	VVIR
Carotid sinus syndrome	DDI

*If chronotropic incompetence is present.

Intermittent conduction abnormalities

Some patients may have been shown to have only occasional conduction abnormalities and sporadic symptoms. Likewise some patients without proven high grade conduction defects may be paced, either because of symptoms, which may be infrequent, or in an effort to improve prognosis. Pacemakers implanted in these patients should have hysteresis selected. It is tempting to use VVI pacemakers in such patients whatever the suspected conduction abnormality, but this can be a grave mistake. It is usual for abnormalities that present as occasional to become more frequent with the passage of time. Furthermore, those paced speculatively for, perhaps occasional syncope caused by suspected intermittent atrioventricular block, may turn out to have the carotid sinus syndrome and while a simple VVI pacemaker may prevent syncope in the former case it is unlikely to do so consistently in the latter.

Patient assessment

Each patient needs to be carefully evaluated before implantation to decide what is the optimal pacemaker. As well as routine clinical assessment a careful electrocardiographic diagnosis of the arrhythmias being treated is obviously necessary. Simple exercise testing may be necessary to determine whether or not the atria are capable of a satisfactory rate response. Ambulatory monitoring may be required in order to make a diagnosis, in order to examine rate response, and also to determine whether any tachycardias are present. Carotid sinus massage or tilt testing is occasionally useful, but electrophysiological testing is rarely necessary.

Conclusions

The correct pacing mode is usually determined by the site of the conduction abnormality and not by the underlying aetiology (table). Three simple rules should be adhered to when chosing the correct pacing mode:

(1) The atrium should be sensed and paced unless contraindicated (chronic atrial arrhythmias or rare anatomical considerations).
(2) The ventricle should be paced if atrioventricular block is present or is likely to develop.
(3) A rate responsive sensor should be added if there is chronotopic incompetence or if atrial activity is abnormal.

Ideally, no patient should receive a constant rate VVI pacemaker. General infirmity may encourage one or more of these rules to be broken, but if the rules are broken for purely budgetary reasons, this should be acknowledged as being the case. Only by doing this will optimal pacing facilities develop, and those in training may then understand clinical decisions to implant less than ideal pacemakers. Although a pacing service has to be provided within a limited budget, any saving made by choosing a cheaper pacing mode has to be set against limitations in the patient's quality and, in some cases, quantity of life. We, and many of our colleagues, do not always keep to our guidelines, but this is purely for fiscal reasons—it is important that we do not try to convince ourselves otherwise. When pacing practice is subjected to medical audit, the clinical outcome may be shown to outweigh any financial arguments.

1 World Survey Data. *PACE* 1987;10:769–77.

2 Bernstein AD, Camm AJ, Fletcher RD, *et al.* The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive-rate pacing and antitachyarrhythmia devices. *PACE* 1987;10:794–9.

3 Senning A. In discussion: Goott B, Miller FA. Prevention of posthypercapneic ventricular fibrillation in dogs. *J Thoracic Surg* 1959;38:630–39.

4 Johnson AD, Laiken SL, Engler RL. Hemodynamic compromise associated with ventriculoatrial conduction following transvenous pacemaker placement. *Am J Med* 1978;65:75–9.

5 Heldman D, Mulvihill D, Nguyen H, *et al.* True incidence of pacemaker syndrome. *PACE* 1990;13:1742–50.

6 Donaldson RM, Fox K, Rickards AF. Initial experience with a physiological, rate responsive pacemaker. *Br Med J* 1983;286:667–71.

7 Rossi P, Aina F, Rognoni G, Occhetta E, Plicchi G, Prando MD. Increasing cardiac rate by tracking the respiratory rate. *PACE* 1984;7:1246–56.

8 Nappholtz T, Valenta H, Maloney J, Simmons T. Electrode configurations for a respiratory impedance measurement suitable for rate responsive pacing. *PACE* 1986;9:960–4.

9 Alt E, Hirgstetter C, Heinz M, Blomer H. Rate control of physiologic pacemakers by central venous blood temperature. *Circulation* 1986;73:1206–12.

10 Foerestrand S, Skadberg BT, Anderson K, Ohm OJ. Acute clinical testing and follow-up of a rate-variable pacemaker controlled by central venous oxygen saturation [abstract]. *J Am Coll Cardiol* 1989;13:112A.

11 Humen DP, Kostuk WJ, Klein GJ. Activity-sensing, rate-responsive pacing: improvement in myocardial performance with exercise. *PACE* 1985;8:52–9.

12 Lau C-P, Tse W-S, Camm AJ. Clinical experience with Sensolog 703: a new activity sensing rate responsive pacemaker. *PACE* 1988;11:1444–55.

13 Lau C-P, Mehta D, Toff WD, Stott RJ, Ward DE, Camm AJ. Limitations of rate responsive of an activity-sensing rate-responsive pacemaker to different forms of activity. *PACE* 1988;11:141–50.

14 Rossi P, Prando MD, Magnani A, Aina F, Rognoni G, Occhetta E. Physiological sensitivity of respiratory-dependent cardiac pacing: four-year follow-up. *PACE* 1988;11:1267–78.

15 Lau CP, Antoniou A, Ward DE, Camm AJ. Reliability of minute ventilation as a parameter for rate responsive pacing. *PACE* 1989;12:321–30.

16 Joseph S, Crowther A, Bahri A, Rose A. Positive fixation electrodes 6–12 years on, a 98% success story [abstract]. *PACE* 1991;14:640.

17 Rubin JW, Frank MJ, Boineau JP, Ellison RG. Current physiologic pacemakers: a serious problem with a new device. *Am J Cardiol* 1983;52:88–91.

18 Shaw DB, Holman RR, Gowers JI. Survival in sinoatrial disorder (sick-sinus syndrome). *Br Med J* 1980;I:139–41.

19 Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;116:16–22.

20 Markewitz A, Schad N, Hemmer W, Bernheim C, Ciavolella M, Weinhold C. What is the most appropriate stimulation mode in patients with sinus node dysfunction? *PACE* 1986;9:1115–20.

21 Attuel P, Pellerin D, Mugica J, Coumel P. DDD pacing: an effective treatment modality for recurrent atrial arrhythmias. *PACE* 1988;11:1647–54.

22 Shandling AH, Feuer JM, Atwood JE, *et al.* The effect of cardiac pacing mode on the long-term development of atrial fibrillation [abstract]. *J Am Coll Cardiol* 1989;13:217A.

23 Sutton R, Kenney R-A. The natural history of sick sinus syndrome. *PACE* 1986;9:1110–4.

24 Furman S, Hayes DL, Holmes DR. *A Practice of Cardiac Pacing.* Mount Kisco: Futura, 1986:60.

25 Rosenqvist M, Ahren C, Norlander R, Ryden L, Schuller H. Atrial rate-responsive pacing—effect on exercise capacity [abstract]. *PACE* 1988;11:514.

26 Rosenqvist M, Obel IWP. Atrial Pacing and the risk for AV block: is there a time for change in attitude? *PACE* 1989;12:97–101.

27 Siddons H. Deaths in long-term paced patients. *Br Heart J* 1974;36:1201–9.

28 Sutton R, Perrins EJ, Morley C, Chan SL. Sustained improvement in exercise tolerance following physiological cardiac pacing. *Eur Heart J* 1983;4:781–5.

29 Boon NA, Frew AJ, Johnston JA, Cobbe SM. A comparison of symptoms and intra-arterial ambulatory blood pressure during long term dual chamber atrioventricular synchronous (DDD) and ventricular demand (VVI) pacing. *Br Heart J* 1987;58:34–9.

30 Fromer M, Kappenberger L, Babotai I. Subjective and objective response to single versus dual chamber pacing. *J Electrophysiol* 1987;1:343–9.

31 Goldreyer BN. Physiologic pacing: the role of AV synchrony. *PACE* 1982;5:613–5.

32 Fananpazir L, Bennett DH, Monks P. Atrial synchronized ventricular pacing: contribution of the chronotropic response to improved exercise performance. *PACE* 1983;6:601–8.

33 Smedgard P, Kristensson BE, Kruse I, Ryden L. Rate-responsive pacing by means of activity sensing versus single rate ventricular pacing: a double-blind cross-over study. *PACE* 1987;10:902–15.

34 Lipkin DP, Buller N, Frenneaux M, *et al.* Randomised crossover trial of rate responsive Activitrax and conventional fixed rate ventricular pacing. *Br Heart J* 1987;58:613–6.

35 Alpert MA, Curtis JJ, Sanfelippo JF, *et al.* Comparative survival after permanent ventricular and dual chamber pacing for patients with chronic high degree atrioventricular block with and without preexistent congestive heart failure. *J Am Coll Cardiol* 1986;7:925–32.

36 Kenny RA, Ingram A, Mitsuoka T, Walsh K, Sutton R. Optimum pacing mode for patients with angina pectoris. *Br Heart J* 1986;56:463–8.

37 Morley CA, Perrins EJ, Grant P, Chan SL, McBrien DJ, Sutton R. Carotid sinus syncope by pacing: analysis of persistent symptoms and role of atrioventricular sequential pacing. *Br Heart J* 1982;42:411–8.

Addendum

Since the submission of this paper, a working party of the British Pacing and Electrophysiology Group have published Recommendations for pacemaker prescription for symptomatic bradycardia (*Br Heart J* 1991;**66**:185–91). We agree with their recommendations and think that our point of view is fully compatible with their's.

Br Heart J 1992;67:289–96

ORIGINAL ARTICLES

Impact of converting enzyme inhibition on progression of chronic heart failure: results of the Munich Mild Heart Failure Trial

Franz X Kleber, Lisa Niemöller, Wittich Doering

Abstract

***Objective*—Neurohormonal activation has major impact on the pathophysiology of congestive heart failure. The Munich Mild Heart Failure Trial was designed to test the hypothesis that interference with the renin-angiotensin system by angiotensin converting enzyme inhibition favourably influences the natural history of heart failure.**

***Design and patients*—170 patients, median New York Heart Association (NYHA) class II, were randomised to double blind treatment with 25 mg captopril twice a day or placebo in addition to standard treatment for a median observation period of 2·7 years.**

***Main outcome measures*—Progression of heart failure to NYHA class IV on an optimally adjusted standard treatment, death due to progressive heart failure, and sudden death.**

***Results*—Heart failure progressed to class IV in nine patients (10·8%) treated with captopril and in 23 patients (26·4%) treated with placebo (p = 0·01). The mean survival time until this end point was 223 days longer in the captopril group (Kaplan-Meier life table analysis; p = 0·02). Also, progressive deterioration to severe heart failure was a powerful predictor of total mortality and death from heart failure; 80% of deaths due to progressive heart failure occurred after this end point. There were fewer deaths caused by progressive heart failure in the captopril group than in the placebo group (4 *v* 11; p = 0·10) but similar numbers of sudden deaths (11 *v* 10). Progressive heart failure was the cause of death in 18·2% of all deaths in the captopril group and 50% in the placebo group. Total heart failure events (the end point on which power calculation was based) were also more common in the placebo group (19 *v* 32 events) but not significantly so. Total mortality was similar to both groups (22 of 83 *v* 22 of 87).**

***Conclusions*—Angiotensin converting enzyme inhibition in conjunction with standard therapy early in the course of congestive heart failure slowed the progress of heart failure and thus favourably altered the natural history of the disease.**

Chronic heart failure is a major cause of morbidity and admission to hospital and has a poor prognosis. Its therapeutic management has two goals: amelioration of symptoms (including improvement in functional capacity) and improvement of prognosis (including influence on progression of congestive heart failure and occurrence of sudden death). Symptoms can be improved by various treatments.[1-3] Knowledge about improvement of prognosis is limited to a few drugs, especially the combination hydralazine and isosorbide dinitrate[4] and converting enzyme inhibitors.[5 6] Factors that have been shown to be associated with unfavourable prognosis in congestive heart failure include an increase in left ventricular volume,[7 8] a low ejection fraction,[9] high filling pressures,[10] low exercise capacity,[9 11] increased activity of the renin angiotensin system,[12] and the sympathetic nervous system[13] as well as low serum sodium concentration[14 15] and an increased concentration of atrial natriuretic peptide.[16] A favourable modification of these variables is therefore a major goal of treatment in congestive heart failure that should accompany symptomatic improvement.[17 18]

In the present trial we aimed to improve outcome by influencing the progression of congestive heart failure by adding captopril to the treatment regimen. We studied patients with mild (minimal to moderate) symptoms and used progression of congestive heart failure to NYHA class IV or death from heart failure as end points.

Patients and methods

STUDY DESIGN

This was a randomised, double blind, placebo controlled, parallel group, single centre trial in patients with congestive heart failure New York Heart Association (NYHA) functional class I–III on standard treatment. To avoid imbalance we randomly assigned patients to treatment with captopril or placebo within four groups defined by the duration of congestive heart failure at entry according to the criteria given below (group 1 up to four weeks, group 2 four weeks to one year, group 3 one year to three years, group 4 over three years). The progress of the study was followed by an independent advisory committee (see appendix I) and the hospital ethics committee also monitored questions of ethical relevance.

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PATIENTS

We studied patients (minimum age 18 years) with congestive heart failure NYHA functional class I, II, or III at entry into the trial. Patients in NYHA functional class IV were excluded. No drugs were stopped before entry. Treatment for heart failure with any drug other than converting enzyme inhibitors was allowed.

DIAGNOSIS OF CONGESTIVE HEART FAILURE

The diagnosis of congestive heart failure was based on history; thorough clinical examination by a cardiologist (usually FK); and laboratory work up, chest '*x* ray', electrocardiography, echocardiography when technically feasible, and either radionuclide ventriculography or coronary angiography with left ventricular cineangiography as clinically appropriate. We excluded patients with underlying cardiac diseases of unknown cause. Diagnosis of congestive heart failure was also confirmed by the presence of the modified Framingham criteria that served as entrance criteria (see below).

ENTRANCE AND EXCLUSION CRITERIA

Our entrance criteria were a slightly modified version of those of McKee *et al* (Framingham Study[19]) (table 1). The entrance criteria were not necessarily imposed at the time of randomisation in patients who had been saved by treatment of heart failure.

BASELINE EXAMINATION AND FOLLOW UP EXAMINATIONS

Baseline examination included cardiac and general history, physical examination, and laboratory and technical work up. Follow up examination included the history taken at regular three-monthly hospital visits. In the case of clinical events additional interim examinations were performed by the investigator. At the regular three monthly visits a standardised questionnaire about cardiac complaints was filled in by the investigators together with the patient. Compliance was checked by a tablet count. At each visit, medication for another three months was given to the patient. A detailed evaluation of follow up symptoms and laboratory results will be presented elsewhere.

TEST MEDICATION, CONCOMITANT MEDICATION, AND GENERAL MEASURES

Captopril and placebo were administered in increasing doses (from 6·25 mg to 25 mg twice a day). When no side effects occurred the maximum dose was reached in three days. The maximum dose was 50% when serum creatinine was >265 μmol/l and 25% when it was >440 μmol/l.

Concomitant medication was introduced and continued according to therapeutic need. No attempt was made by the investigators to influence concomitant medication. If a patient's physician considered that angiotensin converting enzyme inhibitor treatment was necessary we reviewed the patient to see whether heart failure had become severe (the second end point).

Before entry all patients were advised about a moderately salt-restricted diet, weight reduction if necessary, appropriate rest periods, and restricted physical activity. We gave our patients detailed information about the pathophysiology of their disease and its potential sequelae. Psychological reassurance at entry and at each visit was mandatory and a telephone in service staffed by a cardiologist was provided for all patients and family physicians with urgent problems or questions.

END POINTS

Two end points were pre-defined in the study protocol, both end points together were used to calculate the sample size (see Statistical Analysis): death due to heart failure, with subclassification into sudden death (definition see below) and death due to progressive heart failure (definition see below); deterioration of heart failure to severe heart failure (NYHA

Table 1 Entrance criteria and exclusion criteria

Entrance criteria		
Major	*Minor*	*Exclusion criteria*
Paroxysmal dyspnoea or orthopnoea	Ankle oedema	Heart failure NYHA Class IV at entry
Neck vein distension	Night cough	Malignancies or other diseases that greatly affected life expectancy
Rales (more than 10 cm from the base of the lungs)	Dyspnoea on exertion	Haemodialysis or peritoneal dialysis for chronic renal failure
Cardiomegaly on chest *x* ray	Hepatomegaly	Connective tissue diseases
Echocardiographic left ventricular end diastolic diameter more than 60 mm or left ventricular end systolic diameter more than 45 mm	Pleural effusion	Concomitant immunosuppressive therapy
		Known renal artery stenosis
		Gestation and lactation
Acute pulmonary oedema	Tachycardia of at least 120 beats/min	Significant aortic stenosis
S_3 gallop	Weight loss of ≥4·5 kg after introduction of treatment for congestive heart failure where factors other than treatment for congestive heart failure could have contributed to the weight loss	Significant mitral stenosis
Venous pressure > 16 cm H_2O		Myocardial infarction within three weeks
Weight loss of 4·5 kg or more due to introduction of treatment for congestive heart failure		Systolic blood pressure < 95 mm Hg
		Uncontrolled hypertension

Two major or one major and two minor criteria had to be fulfilled.

Table 2 Severity of congestive heart failure at entry

	Captopril	*Placebo*	*p*
Presence of major entrance criteria (%) (mean (SD))	45·8 (21·6)	49·3 (19·2)	NS
Presence of minor entrance criteria (%) (mean (SD))	33·0 (18·6)	34·9 (20·6)	NS
NYHA functional class (% of patients):			
I	27	25	
II	52 } 1·94 (0·69)	48 } 2 01 (0·72)	NS
III	21	26	
Cardiothoracic ratio (%) (mean (SD))	53·6 (5·4)	54·5 (6·8)	NS
M mode echocardiographic diameter (mm) (mean (SD)):			
Diastolic	60·9 (6·7)	63·5 (7·0)	0·027
Systolic	47·9 (9·4)	49·6 (9·0)	NS
Left ventricular ejection fraction*	35·0 (13·1)	34·6 (13·9)	NS
Diuretic score†	3·2 (3·9)	3·6 (4·1)	NS

*By contrast angiography or radionuclide ventriculography.

†Score represents 13·33 mg frusemide or 25 mg hydrochlorothiazide.

functional class IV) despite optimal adjusted concomitant treatment (definition see below).

Before we broke the code all end points were defined and all deaths classified. Sudden death was defined as witnessed unexpected death within an hour of the onset of symptoms, and not occurring in a patient with NYHA class IV heart failure.[20] Death in progressive heart failure was defined as death in cardiogenic shock or pulmonary oedema after a period of severe heart failure. The second end point (deterioration to class IV on optimal concomitant treatment) was defined by the following criteria: congestive heart failure NYHA class IV with symptoms at rest or on minimal exertion in the absence of concomitant problems leading to deterioration (for example, upper or lower airway infections, suboptimal rate control in atrial fibrillation, bradycardia, ventricular extrasystoles compromising pump function). These severe symptoms had to persist despite optimal adjustments of concomitant treatment and recompensation with digitalis, diuretics, nitrates (and hydralazine if appropriate) in suitable doses had to be unsuccessful. A transient deterioration into class IV heart failure that was easily recompensated by standard measures was not accepted as a sufficient end point.

When the end point of class IV heart failure was reached, treatment with captopril (25 mg–50 mg twice a day) was started and mortality follow up was continued (intention to treat). Unwitnessed deaths, other cardiac, cardiovascular, or non-cardiovascular deaths were not categorised. All deaths were reported to the independent advisory committee and all instances of deterioration were verified independently by an end point review board at the request of the advisory committee.

STATISTICS AND SAMPLE SIZE CALCULATION

The results of the Framingham Study, which showed a 37·5% 2·5 year mortality in patients with the first clinical signs of heart failure, led us to expect at least 37·5% heart failure deaths and/or deteriorations to NYHA class IV. We planned to detect a reduction of these events by treatment of 20%–17·5%. The sample size was calculated with an overall type I error rate (alpha) of 0·05 and type II error rate (beta) of 0·20 (Fisher's exact test, two tailed). Under these specified conditions the calculated sample size was 170 patients.

To avoid imbalances in the outlook for the two treatment groups randomisation was stratified by duration of heart failure before the trial. Therefore randomisation was performed in four strata of 100 treatment allocations. Patients were allocated to the next treatment in the stratum depending on their duration of heart failure.

To compare the results in the two treatment groups we used the same statistical method as we used to calculate sample size (Fisher's exact test, two tailed). The overall type I error rate for the comparison of treatment effects on the primary end point (heart failure death and/or progression of heart failure) was fixed at alpha = 0·05.

In addition, we analysed both constituents of the primary end point separately. For this comparison an adjusted alpha type I error rate of alpha = 0·025 was deemed to be significant. The power of a significant test result was calculated on the basis of the appropriate type I error rate.

The confirmatory comparison of the treatment results was performed according to the intention-to-treat approach. In addition to comparisons of crude mortality rates by Fisher's exact test, Kaplan-Meier life table analyses were performed and tested by the generalised Wilcoxon test.

INFORMED CONSENT

Patients were asked to participate at least one day before randomisation after they were given detailed written information. Informed consent was obtained from each patient.

Results

DEMOGRAPHIC DATA

One hundred and seventy patients (128 male

Table 3 Premature treatment withdrawals

Reason	*Captopril (n)*	*Placebo (n)*
Compliance	12	8
Hypotension	6	3
Taste disturbance	1	1
Cough	1	0
Palpitation	1	0
Hypertension*	1	1
Non-cardiac diseases†	2	0

*Because it was impossible to control blood pressure with drugs other than angiotensin converting enzyme inhibitors—that is the other antihypertensive drugs were ineffective or had major side effects.

†Disabling rheumatoid arthritis and severe gastric ulcer in one patient and stroke and inability to swallow in one patient.

Table 4 Heart failure events

End point	*Captopril/placebo*	*p (Fisher's exact test)*
NYHA IV deterioration	9/23	0·010*
Total deaths	22/22	NS
Heart failure deaths:		
Sudden death	11/10	NS
Pump failure death	4/11	0·104
All heart failure events	19/32	0·065
Non-heart failure deaths:		
Reinfarctions	3/0	—
Stroke	1/1	—
Malignancy	1/0	—
Respiratory failure	1/0	—
Pulmonary embolism	1/0	—

*Power = 57% ($\alpha = 0{\cdot}025$).

and 42 female; mean age 62·4) entered the study between February 1985 and October 1989. Patients were randomised to captopril (n = 83) or placebo (n = 87). Most were randomised within group 2 (n = 109; see study design). Patients were followed up for a median of 2·7 years.

AETIOLOGY AND SEVERITY OF CONGESTIVE HEART FAILURE

Coronary artery disease was the leading cause of congestive heart failure, with prior myocardial infarction in 69% (coronary artery disease was the sole reason for congestive heart failure in 58%). Hypertensive heart disease was present in 12% and dilated cardiomyopathy in 20%. Congestive heart failure of other origin was found in 6% of patients. There was atrial fibrillation in 14·7% (25/170) of patients. The percentage of patients with atrial fibrillation was similar in patients in whom progressive heart failure developed (5/32 = 15·6%) or who died later (6/44 = 13·6%). Table 2 shows the severity of congestive heart failure. Most patients had mild symptoms while they were being treated though many had a history of more severe symptoms earlier. NYHA functional classes were evenly distributed among both groups with 72% of patients being in either NYHA class I or II. Left ventricular size and function were well outside the normal range, and the cardiothoracic ratio on the chest x ray was increased. Both groups were very similar except for one echocardiographic variable (table 2).

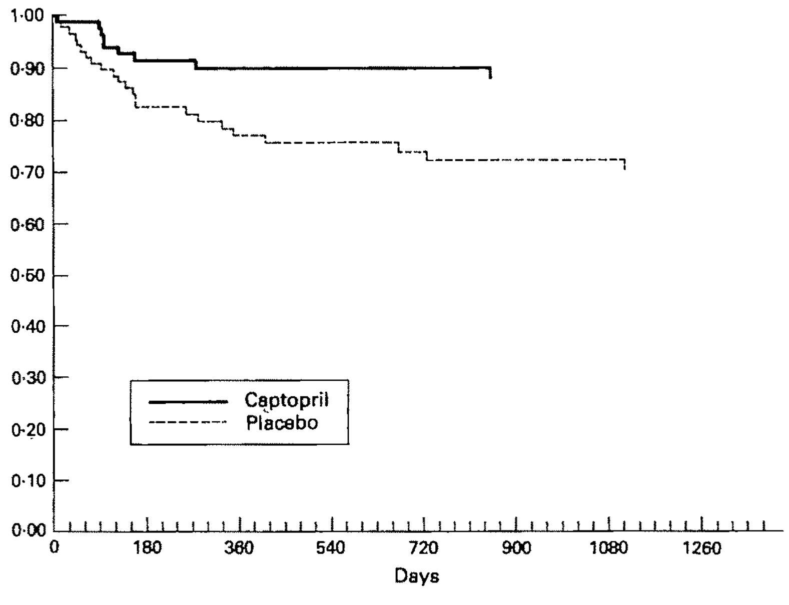

Figure 1 Survival time analysis (Kaplan-Meier) for the end point "progression of heart failure to NYHA class IV on optimal adjusted therapy".

CONCOMITANT MEDICATION AT ENTRY

At entry 78·8% of patients were being treated with diuretic drugs: 42·4% on frusemide (mean dose 81 mg), 27·1% on hydrochlorothiazide (mean dose 35 mg), and 9·3% on other diuretics. At entry, 59% of the patients were taking digitalis treatment (usually digoxin), 59% nitrates, 23% β blockers, 23% antiarrhythmic drugs, and 23% calcium antagonists (usually verapamil) for rate control of atrial fibrillation. All concomitant therapy was evenly distributed at entry in both groups except that nitrates tended to be used more often in the captopril group at entry (59 *v* 41 patients; p = 0·03).

PREMATURE WITHDRAWALS OVER THE TOTAL STUDY PERIOD

A few patients had to be withdrawn from randomised therapy because of side effects, concomitant diseases, or lack of compliance (table 3). Follow up of all patients who were withdrawn from the study was continued for evaluation of end points (intention to treat analysis).

DEATHS

Twenty four (25·9%) patients died, 22 patients in each group, and 81·8% of deaths were due to heart failure: 34·1% to progressive heart failure and 47·7% to sudden death. Other cardiovascular death occurred in 13·6% and noncardiovascular death accounted for 4·5% of all deaths. Table 4 shows the distribution of deaths and other events within the two treatment groups. There was a difference between the groups in death from progressive heart failure but not in sudden death. Half the deaths in the placebo group were due to progressive heart failure but only 18·2% of those in the captopril group. Most non-sudden deaths occurred in hospital and most sudden deaths occurred outside the hospital.

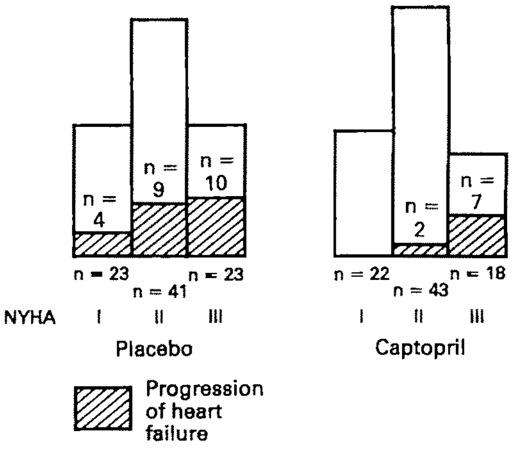

Figure 2 Contribution of patients in different stages of heart failure (according to NYHA functional class at entry) to the group of patients with progression of heart failure (shaded bars) in the placebo and the captopril treated group.

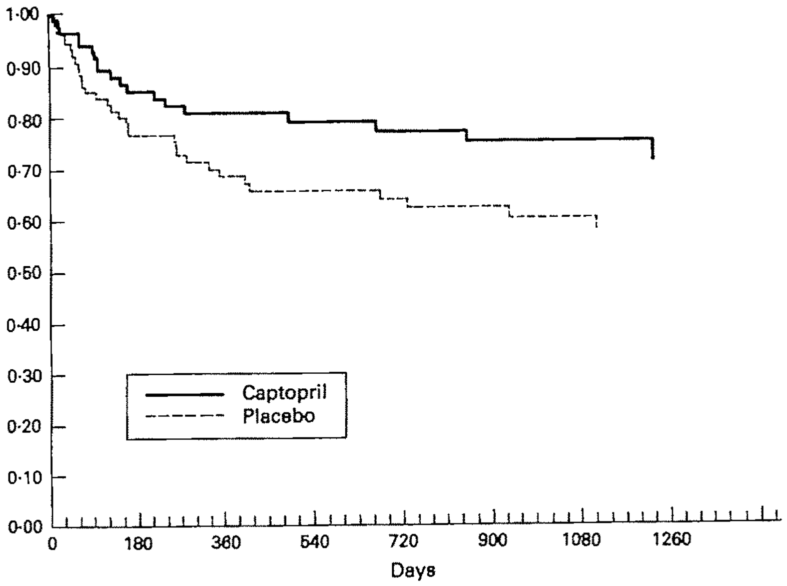

Figure 3 Survival time analysis (Kaplan-Meier) for all heart failure events including death due to progressive heart failure, sudden death, and progression of heart failure to NYHA class IV.

PROGRESSION OF HEART FAILURE TO NYHA CLASS IV

Nearly a fifth (18·8%) of patients experienced severe deterioration to class IV congestive heart failure (end point 2; see methods)—nine patients in the captopril group and 23 patients in the placebo group ($p = 0·011$; power = 0·57; for survival curve see fig 1). Seventeen of these 32 patients died at various times after deterioration (captopril $n = 5$, placebo $n = 12$) while 15 were alive at the end of the study (captopril $n = 4$, placebo $n = 11$). The mean survival time without deterioration to class IV was increased by 223 days in the captopril group ($p = 0·019$). The risk of progression of heart failure continued to be higher on placebo even beyond the observation period of one year (fig 1).

Progression of heart failure to class IV was a powerful predictor of death: 53% of these patients died later compared with 20% of those who did not deteriorate. It was also a predictor of mode of death; 80% of progressive heart failure deaths but only 24% of sudden deaths occurred after deterioration.

Figure 2 shows that the likelihood of progressive heart failure was higher in patients in NYHA class III but that the therapeutic efficacy of captopril was better in NYHA class I/II.

Death due to heart failure or progression of heart failure to NYHA class IV occurred in 19 patients in the captopril group and 32 in the placebo group ($p = 0·065$). Figure 3 shows the survival curve for the combination of both end points. The mean event-free survival time in this analysis was prolonged by 292 days (life table p level = 0·071). Table 5 gives the cumulative event rate for both end points after a year and at the end of the study.

Discussion

DEMOGRAPHIC DATA

This study followed 170 patients for a median observation period of 2·7 years (three months to five years). The main question of the trial was whether addition of angiotensin converting enzyme inhibitors to standard treatment might favourably influence the prognosis of congestive heart failure. Progression of heart failure to refractory NYHA class IV or death due to heart failure were defined. Patients in both groups were similar with respect to age, observation period, heart and left ventricular size, and NYHA class, as well as concomitant treatment.

PROGNOSTIC CRITERIA

When this trial was designed in 1984 an end point in addition to death was planned for two reasons: by 1984 symptoms of severe heart failure had already been shown to be improved by angiotensin converting enzyme inhibition in several trials[21–23] and we thought that for this reason angiotensin converting enzyme inhibitor treatment should not be withheld from these patients. This point of view was confirmed by the results of the CONSENSUS trial[5] and made a later protocol amendment for ethical reasons unnecessary. Though not good,[19] prognosis in mild congestive heart failure is much better than in severe congestive heart failure,[10 24] and the transition of mild forms to the most severe forms had to be recognised as a prognostically important deterioration.

The introduction of additional end points can reduce sample size, but additional end points are less reliable indicators of extended life expectancy than death itself. However, there are several well recognised determinants of poor prognosis in congestive heart failure,[9] that have been proposed for prognostic studies and are being used as additional end points in ongoing trials (SAVE trial, M Pfeffer, personal communication). We used NYHA class IV heart failure as an additional end point. NYHA class IV heart failure is defined more unequivocally and inter-observer disagreement does not occur as often as with the other grades of severity. To define NYHA class IV even more strictly we added the term "under optimal adjusted concomitant therapy."

The introduction of a second end point into a prognosis trial, however, implies that death

Table 5 Cumulative event rate (%) (Kaplan-Meier analysis) at one year of follow up and at the end of the study

Observed end point	*One year Captopril/placebo*		*End of study Captopril/placebo*		*p (life table)*
Progression of heart failure to NYHA IV under optimal adjusted concomitant therapy	10·1	23·0	12·2	30·3	0·0108
Death	16·4	4·6	37·8	39·8	NS
Heart failure, death, or NYHA IV	19·0	28·4	31·3	42·1	0·0712

after the first end point (after deterioration to NYHA class IV) regularly occurs after the start of active treatment (that is, with an angiotensin converting enzyme inhibitor). Thus analysis on the basis of intention to treat might be appropriate for the first end point only.

END POINTS

Mortality

In the placebo group one year mortality was 15%, two year mortality 19%, three year mortality 25% and five year mortality was 40%. These data show a lower mortality than in the Framingham study,[19] which is in part explained by the introduction of angiotensin converting enzyme inhibitor treatment after the occurrence of the end point of NYHA class IV heart failure (see below).

Overall mortality was not different in our two treatment groups. There are several explanations for this: patients reaching the second end point (deterioration to NYHA class IV) were regularly switched to active treatment. Treatment with angiotensin converting enzyme inhibitor therapy in class IV heart failure has been shown to reduce mortality[5] and this would obscure the effects on mortality in our trial. Patients with congestive heart failure are threatened by two major causes of death: sudden death and death due to progressive heart failure. Sudden death in our trial was not influenced by captopril (see below) and it was the major mode of death (see below).

The calculated sample size in this trial (170 patients) was based on heart failure events including deteriorations and deaths due to heart failure. This study does not have enough power to demonstrate effects on mortality alone or mortality due to specific causes (for example, sudden death).

Sudden death

Angiotensin converting enzyme inhibitors might decrease the likelihood of sudden death by improving left ventricular function, by decreasing filling pressures and peripheral vascular resistance, by avoiding potassium and magnesium deficits, and by the effects on reperfusion arrhythmias (shown experimentally).[25] In our trial, however, we found that captopril did not affect sudden death. Eleven sudden deaths occurred in the captopril group and 10 in the placebo group. This lack of difference on sudden cardiac death could be attributed to the low dose of captopril we administered. Trials that showed a significant reduction in ventricular extrasystoles by angiotensin converting enzyme inhibitor treatment[26-28] used higher doses. However, serum potassium concentrations increased significantly in the captopril group but not in the placebo group, and the increase in noradrenaline with increasing severity of congestive heart failure was blunted in patients treated with captopril (unpublished data). These observations support the suggestion that the dose of 25 mg twice a day is an effective dose. Thus our trial suggests that the potential of angiotensin converting enzyme inhibitors to prevent sudden cardiac death might have been overestimated. The results of the CONSENSUS trial[5] accord with this.

Death due to progressive heart failure

Death due to progressive heart failure occurred more often in the placebo group than in the captopril group (4 *v* 11 patients). This difference was not significant (p = 0·10); however, the subset of patients studied was small.

Progression of heart failure to NYHA Class IV

Severe worsening of heart failure was considerably suppressed by captopril treatment. Deterioration to NYHA class IV has prognostic relevance,[10 24 29] and avoidance of decompensation by non-pharmacological means has been shown to improve outcome.[30] The introduction of active treatment at this point, however, obscured the influence on mortality. Nevertheless, captopril significantly prevented both symptomatic deterioration and life-threatening progression of disease.

Furthermore, progression to class IV heart failure was a powerful predictor of outcome. Mortality in this subset was 2·5 times higher than in the remaining patients. Deterioration to class IV was also most predictive for death in progressive heart failure, whereas it was not a good predictor of sudden death. Only five of the 21 patients who died suddenly died after deterioration of heart failure. Overall this suggests that our definition of deterioration of heart failure to class IV on optimal adjusted concomitant treatment can serve as a surrogate for death from progressive heart failure and obviously reflects progression of heart failure.

Captopril was more effective in preventing the progression of heart failure in patients with NYHA class I or II at entry than in patients with NYHA class III. About half the patients in whom the disease progressed had heart failure in NYHA class III at entry (fig 2).

Possibly because many patients reached end point 2 (almost as many as reached end point 1) a considerable number of patients died after active treatment was started. This was 2·5 times more common in the placebo group than in the captopril group. This reduced the difference between the two groups so that the difference in the combined end points was not significantly different (life table p = 0·071, Fisher's exact test p = 0·065).

Progression of heart failure is associated with progressive left ventricular dilatation,[8 31] which in turn is associated with outcome.[18 31 32] Though several experimental[33 34] and clinical[35 36] trials showed that angiotensin converting enzyme inhibition had a beneficial effect on progressive left ventricular dilatation after myocardial infarction our trial does not establish or confirm the hypothesis that progression of heart failure is necessarily due to progressive pump dysfunction or left ventricular dilatation. It does, however, show that progressive heart failure is a predictor of poor outcome and that progression of heart failure can be influenced favourably by angiotensin converting enzyme inhibition. Thus earlier treatment of congestive failure with converting enzyme inhibitors offers therapeutic benefits over and above the standard treatment of refractory congestive heart failure.

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LIMITATIONS OF THIS TRIAL

This trial aimed to improve outcome in heart failure (reduction of deaths due to heart failure and slowing of progression of heart failure). The study design and sample size prevented our investigating the hypothesis that angiotensin converting enzyme inhibitors improve survival longevity whatever the cause of death. Furthermore, part of the crucial difference occurred in an end point that might be viewed as less reliable than death. However, the difference in death due to progressive heart failure (11/87 *v* 4/83) and in deterioration to class IV heart failure (23/87 *v* 9/83) was considerable and was the reason why the advisory committee discouraged a double blind extension of this study. Deterioration to class IV is not an ideal index of progression of heart failure. However, progressive symptoms despite optimal concomitant therapy characterise the relentless deteriorating course of congestive heart failure and therapeutic strategies designed to avoid decompensations of congestive heart failure have been shown to improve considerably prognosis in an open trial.[30]

Our study did not aim to demonstrate improvement in exercise capacity, because several randomised controlled studies have already consistently shown a positive effect of angiotensin converting enzyme inhibition on exercise capacity.[21 23 37] Meanwhile, however, exercise time has been shown to be an independent predictor of mortality,[9] which strengthens the interest in exercise capacity. This study is limited because exercise time and maximal oxygen consumption were not measured. It is unlikely that improvement in exercise capacity is a measure of symptomatic benefit or of prognostic relevance in patients in NYHA class I and II (that is 72% of our patients) because these patients are largely symptomfree in everyday life.

We studied patients in NYHA functional classes I, II, and III, which introduced some heterogeneity into the population under investigation. The entrance criteria did not include NYHA class, but were derived from the Framingham criteria and the inclusion of patients with dissimilar severity gave the opportunity to study treatment efficacy in various subgroups. The mean and median NYHA class II and the relatively low one year mortality rate (15%) are typical of a population with fairly mild heart failure, though patients with moderate heart failure were definitely included as well.

The results of the CONSENSUS trial and the present study make it unlikely that treatment with converting enzyme inhibitor influences sudden death. Neither had enough power, however, to demonstrate a lack of influence on sudden death alone, rather than progressive heart failure. It might be more appropriate and more ethical to study patients with left ventricular dysfunction without overt heart failure to further investigate this question.

This trial was performed at one hospital. Though bias in the assignment of end points is not possible in a double blind trial, personal errors have more effect than in a multicentre trial. However, the critical end point "deterioration to NYHA class IV" was reevaluated by an independent review board. A monocentre trial is more likely to be consistent in terms of evaluation methods and diagnostic criteria.

We conclude that angiotensin converting enzyme inhibitor treatment in conjunction with standard treatment slows the progress of congestive heart failure and thus is able to improve prognosis, though it does not reduce the risk of sudden cardiac death. Because of the design of our study we do not know whether overall mortality is influenced by these drugs in mild congestive heart failure. Three trials are underway to answer this question: the V-HeFT II, the SOLVD, and the SAVE trial. Our results indicate that angiotensin converting enzyme inhibitor treatment should be considered for any patient who requires medical treatment for symptomatic congestive heart failure.

We thank the members of the advisory committee (see appendix I) and the review board (see appendix II) as well as the former chief of the division, Dr Erwin König, for advice and support. We also greatly appreciate the cooperation of the other medical divisions at our institution and also their physicians in chief, Dr Helmut Mehnert, Dr Horst Kuhlmann, Dr Werner Kaboth, Dr Dieter Eichenlaub; the organisational assistance of Mrs Evelyn Hitzke; and the secretarial expertise of Ms Patricia Hodges. We thank the nurses and technicians of the Krankenhaus München-Schwabing for their support and for sharing in our enthusiasm.

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1 The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539–44.
2 DiBianco R, Shabatai R, Kostik W, Moran J, Schlant T, Wright R, for the Milrinone Multicentre Trial Group. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989;320:677–83.
3 Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987;57:17–22.
4 Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study. *N Engl J Med* 1986;314:1547–52.
5 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429–35.
6 Newmann TJ, Maskin CS, Dennick IG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *Am J Med* 1988; 84(suppl A):140–4.
7 Jeremy RW, Allmann KC, Bautowich G, Harris PJ. Patterns of left ventricular dilatation during the six months after myocardial infarction. *J Am Coll Cardiol* 1989;13:304–10.
8 Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease; Selection by univariate and multivariate analyses from the clinical electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation* 1979;59:421–30.
9 Cohn JN, Archibald DG, Francis GS, Ziesche S, Franciosa JA, Harston WE, *et al.* Veterans Administration cooperative study of vasodilator therapy of heart failure: influence of pre-randomization variables on the reduction of mortality by treatment with hydralazine and isosorbide dinitrate. *Circulation* 1987;75(suppl IV):49–54.
10 Franciosa JA. Why patients with heart failure die: hemodynamic and functional determinants of survival. *Circulation* 1987;75(suppl IV):20–7.
11 Gradman A, Deedwania P, Cody R, Massie B, Packer M, Pitt B, *et al*, for the Captopril-Digoxin Study Group. Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol* 1989;14:564–70.
12 Rockman HA, Juneau C, Chatterjee K, Rouleau JR. Long-term predictors of sudden and low output death in chronic congestive heart failure secondary to coronary artery disease. *A J Cardiol* 1989;164:1344–8.
13 Cohn JN, Levine B, Olivari MT, Garberg V, Lura D, Francis GS, *et al.* Plasma norepinephrine as a guide to

prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:891–923.

14 Lee WH, Packer M. Prognostic importance of serum sodium concentrations and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;73:257–67.

15 Packer M, Medina N, Yushak M. Correction of dilutional hyponatremia in severe chronic heart failure by converting-enzyme inhibition. *Ann Intern Med* 1984;100:782–9.

16 Gottlieb SS, Kukin ML, Ahern D, Packer M. Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. *J Am Coll Cardiol* 1989;13:1534–9.

17 ACE inhibitors after myocardial infarction. *Lancet* 1989;ii:1133–4.

18 Kleber FX. ACE Inhibitors after myocardial infarction. *Lancet* 1990;i:295, 984.

19 McKee PA, Castell WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441–6.

20 Hinkle LE Jr, Tzvi Thaler H. Clinical classification of cardiac deaths. *Circulation* 1982;65:457–64.

21 Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983;2:755–63.

22 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, *et al*. Captopril in heart failure: a double blind controlled trial. *Br Heart J* 1984;52:530–5.

23 Kramer BL, Massie BM, Topic N. Controlled trial of captopril in chronic heart failure: a rest and exercise hemodynamic study. *Circulation* 1983;67:807–16.

24 Wilson JR, Schwartz JS, St John Sutton M, Ferraro LN, Horowitz N, Reichel N, *et al*. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;3:403–10.

25 van Gilst WH, de Graeff PA, Wesseling H, de Langen CDJ. Reduction of reperfusion arrhythmias in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: a comparison of captopril, enalapril, and HOE 498. *J Cardiovasc Pharmacol* 1986;8:722–8.

26 Cleland JGF, Dargie HJ, Ball SG, Gillen G, Hodsman GP, Morton JJ, *et al*. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985;54:305–12.

27 de Langen CDJ, de Graeff PA, van Gilst WH, Bel KJ, Kingma JH, Wesseling H. Effects of angiotensin II and captopril on inductible sustained ventricular tachycardia two weeks after myocardial infarction in the pig. *J Cardiovasc Pharmacol* 1989;13:186–91.

28 Webster MWI, Fitzpatrick MA, Nicholls MG, Ikram H, Wells E. Effect of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol* 1985;56:566–9.

29 Chatterjee K, Parmley WW, Cohn JN, Levine TB, Awan NA, Mason DT, *et al*, for the Captopril multicenter research group. A cooperative multicenter study of captopril in congestive heart failure: hemodynamic effects and longterm response. *Am Heart J* 1985;110:439–47.

30 Bertel O, Conen D, Schwarz U, Besch W, Dubach UC. Verbessert die engmaschige Kontrolle und Therapie-Anpassung die Prognose bei schwer herzinsuffizienten Patienten? *Schweiz Med Wochenschr* 1985;115:1820–3.

31 Kleber FX, Einwang HP, Kronski D, Ohly A, Osterkorn K, Doering W. Progrediente linksventrikuläre Dilatation nach Vorderwandinfarkt als Determinante für die Entwicklung einer Herzinsuffizienz. *Z Kardiol* 1990;79:1–7.

32 White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44–51.

33 Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. *Circulation* 1985;72:406–12.

34 Sweet CS, Emmert SE, Stabilito II, Ribeiro LG. Increased survival in rats with congestive heart failure treated with enalapril. *J Cardiovasc Pharmacol* 1987;10:636–42.

35 Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med* 1988;319:80–6.

36 Sharpe N, Smith H, Murphy J, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1988;i:255–9.

37 Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation* 1984;70:271–8.

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Limitations of transoesophageal echocardiography in patients with focal cerebral ischaemic events

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Abstract

Objective—To investigate the detection rate of cardiac sources of embolism by transoesophageal echocardiography in patients with focal cerebral ischaemic events and to relate the echocardiographic findings to other clinical findings.

Design—Prospective study with blinded analysis of the echocardiographic data and subsequent comparison with the other clinical findings.

Setting—Regional cardiothoracic unit based in a teaching hospital.

Patients—131 consecutive patients with focal ischaemic cerebral events (49 with a transient ischaemic attack, 77 with a cerebrovascular accident, and five with a retinal arterial embolus) referred for echocardiography.

Interventions—Full M mode, cross sectional, Doppler, and contrast echocardiography by both the precordial and transoesophageal techniques.

Results—Precordial echocardiography detected a cardiac abnormality in 72 patients. Transoesophageal echocardiography confirmed all the precordial findings (except left ventricular hypertrophy, which at present cannot be defined with this technique) and detected other abnormalities in a further 20 patients (18 with potential right-to-left shunts and two with valve vegetations). It also showed spontaneous contrast echoes in 27 of 28 patients with a large left atrium and showed atrial thrombus in three. Cardiac abnormalities were clinically detected in 53 patients, all of which were confirmed or documented by echocardiography. In the 78 patients with no clinically detectable cardiac abnormality six had mitral valve prolapse and one had a regional wall motion defect (identified by precordial echocardiography) and 17 had potential right-to-left shunts (11 of which were identified only by transoesophageal echocardiography).

Conclusions—Transoesophageal echocardiography is more sensitive than precordial echocardiography in detecting potential sources of embolism in these patients. However, except for the detection of a potential right-to-left shunt, the yield in patients with no cardiac abnormality is low. Moreover, the abnormalities detected in those with previously detected cardiac disease merely confirm the clinical diagnosis. Patients with left atrial spontaneous contrast echoes may benefit from anticoagulation but this requires further study. Until more data are available on this feature and on the role of potential right-to-left shunts in this population, the contribution of echocardiography, precordial or transoesophageal, remains limited.

Clinical studies suggest that emboli arising from the heart cause 5–20% of focal cerebral ischaemic events.[1–3] Necropsy data suggest that emboli may be responsible for up to 50% of fatal events.[4 5] Though these data may suggest that cardioembolic events are more often fatal than other causes of focal cerebral ischaemia, another interpretation is that it is difficult to detect cardiac sources of emboli in patients who have focal cerebral events. The development of M mode and cross sectional echocardiography has enhanced our ability to detect cardiac abnormalities in these patients,[6–8] but the sensitivity and specificity of these methods for the detection of potential embolic sources (for example, thrombi) are not known. In this group of patients precordial echocardiography has other deficiencies. Firstly, in quite a few it is not possible to obtain adequate images. Secondly, abnormalities that are detected (for example, rheumatic mitral valve disease) have usually been detected clinically. Although the image quality in such cases is inadequate for the detection of the associated left atrial thrombus, the presence of the latter is assumed and the patient is treated with oral anticoagulants. Lastly, the detection of an abnormality does not prove a pathogenic mechanism for the neurological event.

The development of transoesophageal echocardiography[9] allows evaluation by high frequency ultrasound of the left atrium including its appendage, areas that are not imaged well from the precordium.[10 11] The left atrial appendage in particular is a common site for thrombus[12 13] and the transoesophageal technique has proved useful for its detection.[14]

Although some workers have reported on the enhanced detection of cardiac sources of emboli with transoesophageal echocardiography,[15–17] many of the limitations of precordial echocardiography in this group of patients also apply to the transoesophageal technique and it is not clear what impact this imaging method will have on decisions about treatment in individual patients. This study was therefore performed prospectively to evaluate the information provided by transoesophageal echocardiography in relation to earlier clinical information in a series of patients presenting acutely with a focal cerebral ischaemic events. Patients presenting with any of the following were considered for study: transient ischaemic attack, reversible ischaemic neurological deficit, cerebrovascular accident, or retinal arterial occlusion.

Patients and methods

PATIENTS

We studied 131 consecutive patients with a recent focal neurological ischaemic event who were referred for echocardiography. Echocardiography was performed within two weeks of the presenting neurological event in all cases. Before echocardiography, relevant details of the history and clinical examination were recorded. The underlying cardiac rhythm was recorded and the case notes examined for evidence of paroxysmal arrhythmias. A raised blood pressure on presentation was not taken as evidence of hypertension, which was defined as (*a*) blood pressure requiring specific antihypertensive medication before the presenting event or (*b*) raised pressures on admission that persisted for more than a week, either associated with electrocardiographic evidence of left ventricular hypertrophy or requiring antihypertensive treatment. Cerebrovascular disease was defined as the presence of a carotid bruit (10 patients), Doppler evidence for an internal carotid stenosis (four patients), or cerebral angiographic evidence of a vascular abnormality consistent with the presenting event (two patients). Duplex studies of the carotid arteries were not routinely performed in these patients. A past history of myocardial infarction and confirmatory electrocardiographic evidence were noted. To be a risk factor for the presenting event, the myocardial infarction had to have occurred in the three months before the neurological episode. Clinical diagnoses of infective endocarditis, hypertrophic cardiomyopathy, and dilated cardiomyopathy were recorded.

All patients with a cerebrovascular accident had been previously assessed by a consultant neurologist or senior physician in our centre. All such patients had undergone computed axial tomography of the head. Patients with cerebral haemorrhage or space-occupying lesions were excluded. The protocol had the full agreement of the local ethics research committee.

PRECORDIAL ECHOCARDIOGRAPHY

All patients had full M mode and cross sectional echocardiography in standard imaging planes, with relevant Doppler studies within two weeks of the presenting neurological event. A Hewlett-Packard 77020 or 77030A ultrasound system was used, series Sonos 500 or 1000. Images were obtained with a 3·5 MHz transducer, but if these were suboptimal a 2·5 MHz transducer was used. Standard measurements of the left atrium and ventricles were made and ventricular function was assessed. Mitral valve prolapse was defined according to the clinical and echocardiographic criteria described by Perloff and colleagues.[18] At the end of the routine study a precordial contrast echocardiogram was obtained. An 18G Venflon (Viggo Products, Helsingborg, Sweden) was inserted into a left antecubital vein. With 10 or 20 ml syringes, 1-2 ml of blood was drawn into the syringe and 8–18 ml of physiological saline was added. Air was drawn into the syringe and the solution agitated either by vigorous shaking or by rapidly injecting it between two syringes via a three-way tap. The air and macrobubbles were then expelled and the resultant solution containing microbubbles was injected rapidly. Recordings of an M mode study across the mitral valve during the injection were made on video tape and a hard copy print out was obtained. Cross sectional images were recorded on video tape in the apical four-chamber view or if this was unsatisfactory in a subcostal four chamber view. Recordings of the contrast studies were made before and during a Valsalva manoeuvre. The release phase of the manoeuvre coincided with the arrival of contrast in the right atrium.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

The transoesophageal study was performed immediately after or, if this was not possible, within three days of the precordial study. The patient was fasted for four hours before the study which was performed in the left lateral position with topical hypopharyngeal anaesthesia (10% lignocaine solution) and, in a few patients, mild sedation (2·5–10 mg midazolam).[19] After a complete anatomical examination the transducer was positioned with the scanning plane at the level of the atrial appendage. The gain and compression controls were modified to enhance weak echoes, thus optimising the ability to detect spontaneous contrast echoes (fig 1). The transducer was then rotated so that the scanning plane was at the level of the foramen ovale. Colour flow mapping was performed to evaluate the possibility of a shunt across the atrial septum. After this a contrast study was performed both before and during a Valsalva manoeuvre as described above. The following diagnostic definitions were used:

(*a*) *Mitral valve prolapse*—superior systolic displacement of the anterior or anterior and posterior leaflets above the level of the mitral annulus as seen in the four chamber view, irrespective of the position of the coaptation point or superior displacement of the posterior annulus together with superior displacement of the coaptation point.

(*b*) *Atrial septal defect*—evidence of left-to-right shunting on colour flow mapping or a "negative" right atrial contrast study irrespective of the detection of an anatomical defect in the atrial septum on two dimensional imaging alone.

(*c*) *Patent foramen ovale*—Anatomically intact atrial septum, no left-to-right shunting on colour flow mapping, right-to-left shunting detected on contrast study or by colour flow mapping (fig 2).

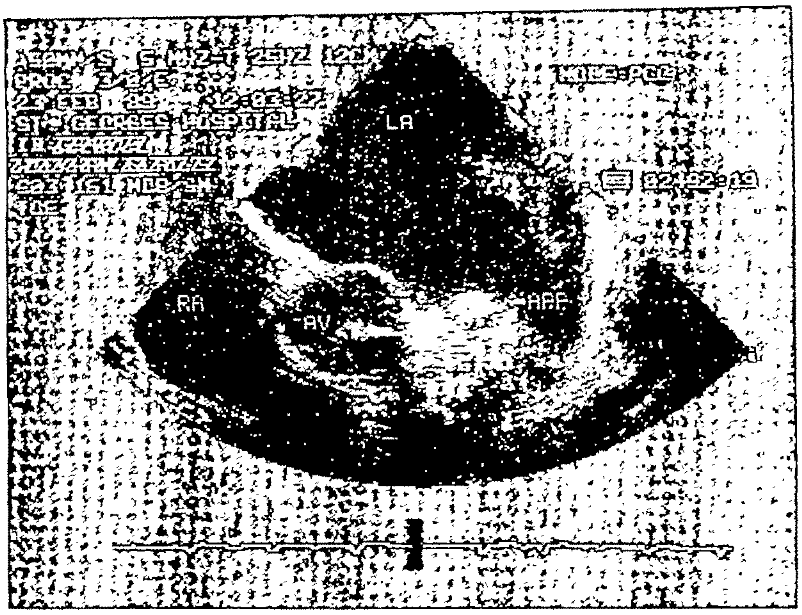

Figure 1 Cross sectional transoesophageal echocardiogram of the left atrium and its appendage. There was a wisp-like cloud of spontaneous contrast echoes (which were seen more clearly during real time echocardiography) in the the appendage (arrow heads). LA, left atrium; APP, appendage; AV, aortic valve; RA, right atrium.

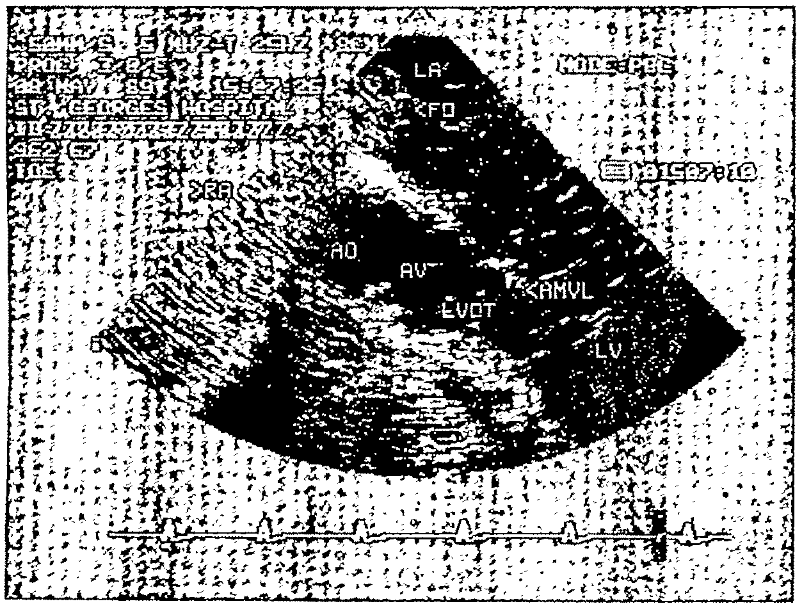

Figure 2 Cross sectional transoesophageal echocardiogram during a contrast study with the imaging plane at the level of the atrial septum. There was a cloud of echoes from microbubbles in the right atrium. Some microbubbles were detected passing across the atrial septum to the left atrium. Some of these had passed through the left ventricle and were seen passing from the left ventricular outflow tract to the aorta. LA, left atrium; RA, right atrium; FO, atrial septum at the level of the foramen ovale; LV, left ventricle; LVOT, left ventricular outflow tract; AMVL, anterior mitral valve leaflet; AV, aortic valve; AO, aorta.

(*d*) *Pulmonary arteriovenous fistula*—As for patent foramen ovale, except that no evidence of right-to-left shunting was detected across the atrial septum. Instead contrast was seen to pass into the left atrium from the direction of the right pulmonary veins and was detected only after a period of three or more cardiac cycles from the appearance of contrast in the right atrium—in all such cases the microbubbles detected were considerably smaller than those seen to pass immediately across the atrial septum in definitions (*b*) and (*c*) above.

The left ventricular wall thickness was not measured in the transoesophageal studies. The short axis view from the stomach transects the ventricle at papillary muscle level. We have noted that the ventricular wall appears thicker at this level by the transoesophageal technique than it does with standard measurements from the precordial studies (measured above the papillary muscles); no satisfactory normal data are yet available and it is thus difficult to confirm the presence of ventricular hypertrophy with the transoesophageal transducer.

INTERPRETATION OF ECHOCARDIOGRAPHY STUDIES

All hard copy print outs and video tapes were analysed by an experienced interpreter (GL) who was blinded to the interpretation of the operator performing the studies. Although this interpreter knew that all patients had had a neurological event, he was unaware of the other clinical details of the patient. Results were compared with the interpretation of the operator. Agreement was complete in all patients except two with a possible pulmonary arteriovenous fistula as defined above; the operator had detected a shunt during the study but this was not confirmed in the subsequent analysis. These patients were recorded as having no shunt.

Results

The mean age of the 131 patients was 57 years (range 20–88 years) and 77 (59%) were men. Forty one patients (31%) were smokers at the time of presentation, 17 (13%) were ex-smokers, and 73 (56%) were non-smokers. The presenting event was a transient ischaemic attack in 49 patients (eight with a history of previous events), a cerebral infarct in 77 (four with a previous history), and in five a retinal arterial occlusion had occurred (one patient with amaurosis fugax and four with persistent visual defects). The "risk factors" of the five patients with retinal artery occlusion were mitral valve prolapse (one patient), known cerebrovascular disease (one patient), hypertension (one patient) and no clinically detectable factor (two patients, one with mitral annular calcification on echocardiography).

Table 1 shows the echocardiographic findings with the precordial and transoesophageal techniques in relation to the clinically determined risk factor(s) for the neurological event.

PATIENTS WITH HYPERTENSION ALONE

Sixteen patients were being treated for hypertension on presentation: eight had left ventricular hypertrophy. No other abnormalities were detected in this group.

PATIENTS WITH ATRIAL FIBRILLATION (OTHER RISK FACTORS EXCLUDED)

Sixteen patients had atrial fibrillation (11 chronic, five paroxysmal). All five patients with paroxysmal atrial fibrillation were in sinus rhythm during the echocardiographic studies. Precordial echocardiography showed a large left atrium in 10, all with chronic fibrillation. Transoesophageal echocardiography showed spontaneous contrast echoes in and around the left atrial appendage in nine of these 10 patients: in five, these echoes were also seen in

Table 1 Echocardiographic findings in relation to risk factors for focal cerebral event

	Echocardiographic findings									
	LVH		*Large LA/SCEs*		*MVP*		*PFO/ASD (PAVF)*		*Other*	
Risk factor(s) for event (n)	*PCE*	*TOE*	*PCE*	*TOE**	*PCE*	*TOE*	*PCE*	*TOE*	*PCE*	*TOE*
Hypertension (16)	8	?	—	—	—	—	—	—	—	—
Chronic/paroxysmal atrial fibrillation† (16)	—	—	10	9	—	—	1	2 (1)	1 AS aneurysm	
Cerebrovascular disease (12)	—	—	—	—	1	1	—	2	—	—
Rheumatic mitral valve disease/ MVR (12)	—	—	11	11	—	—	—	2 (1)	—	1 vegns
MI/DCM/HCM (8)	1	?	3	3	—	—	—	1	6 RWMA	
Mitral valve prolapse (4)	—	—	—	—	4	4	1	1	—	—
Combinations‡ (10)	4	?	3	3	—	—	1	4	2 RWMA	
Other‡ (12)	2	?	1	1	—	—	2	4		1 AV vegns
None (41)	—	—	—	—	5	5	4	11 (1)	1 bicuspid AV 1 RWMA 1 MAC	
Total (131)	15	?	28	27	10	10	9	27 (3)	—	—

PCE, precordial echocardiography; TOE, transoesophageal echocardiography; LVH, left ventricular hypertrophy; LA, left atrium; SCEs, spontaneous contrast echoes; MVP, mitral valve prolapse; PFO, patent foramen ovale; ASD, atrial septal defect; PAVF, pulmonary arteriovenous fistula; AS, atrial septal; MVR, mitral valve replacement; vegns, vegetations; MI, recent myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RWMA, left ventricular regional wall motion abnormality; AV, aortic valve; bicsp, bicuspid; MAC, mitral annular calcification.

*Numbers refer to TOE studies in which spontaneous contrast echoes were seen.

†Without evidence of mitral valve disease, hypertension, or recent infarction.

‡See text.

? Wall thickness measurements from transoesophageal studies not made (see text).

the main left atrial chamber. Both precordial and transoesophageal echocardiography showed an aneurysm of the atrial septum in one patient. The right-to-left shunt from an atrial septal defect was shown in one patient by precordial echocardiography but left-to-right shunting was only demonstrated on the transoesophageal colour flow map. A patent foramen ovale was shown in one patient and a pulmonary arteriovenous fistula in another only by transoesophageal echocardiography.

PATIENTS WITH CEREBROVASCULAR DISEASE

The heart was echocardiographically normal in nine of 12 patients who had evidence of cerebrovascular disease. One patient had mitral valve prolapse and two had evidence of right-to-left shunting across a patent foramen ovale, which was detected only with a transoesophageal contrast study.

PATIENTS WITH RHEUMATIC MITRAL VALVE DISEASE OR PREVIOUS MITRAL VALVE REPLACEMENT

Eleven of the 12 patients in this group were in atrial fibrillation. All eleven had a large left atrium as determined by precordial echocardiography and spontaneous contrast echoes shown by transoesophageal echocardiography. Three patients had echogenic masses in the left atrium consistent with thrombus. In one the thrombus was seen in the atrial appendage only, in another it extended from the appendage across the roof of the atrium, and in the third it was visualised on the posterior wall of the atrium adjacent to the right upper pulmonary vein. A clinical diagnosis of mitral prosthetic endocarditis was made in one patient who had two transient ischaemic episodes three months after mitral valve replacement. Blood cultures (which subsequently proved positive) had been taken before echocardiography which showed echoes consistent with mitral valve vegetations. Two patients had evidence of a patent foramen ovale and one had a presumed pulmonary arteriovenous fistula; all of these were only apparent on the transoesophageal studies.

PATIENTS WITH A RECENT MYOCARDIAL INFARCT OR CARDIOMYOPATHY

A regional wall motion abnormality was detected in all six patients who had had a Q wave infarct in the three months before the presenting event. One of these patients had a large left atrium, as did one patient with dilated cardiomyopathy and the patient with hypertrophic cardiomyopathy. In these three patients spontaneous contrast echoes were shown in the left atrium on the transoesophageal study. In addition, spontaneous contrast echoes were visualised in the left ventricle of the patient with dilated cardiomyopathy and the patient with the previous infarct. A patent foramen ovale was shown by transoesophageal echocardiography in one patient with a previous infarct.

PATIENTS WITH MITRAL VALVE PROLAPSE

Four patients had clinical diagnoses of mitral valve prolapse; all were confirmed on echocardiography. One of these patients also had a patent foramen ovale.

PATIENTS WITH COMBINATIONS OF THE ABOVE RISK FACTORS

Twelve patients had combinations of risk factors—for example, hypertension and atrial

Table 2 Summary of echocardiographic findings in patients with and without clinically detected cardiac abnormalities

		*Echocardiographic findings**			
	No	*MVP*	*Large LA or SCEs*	*R-to-L shunt*	*Other*
Patients with no clinical cardiac abnormality	78	6	0	17	1 RWMA 1 MAC
Patients with clinically detected cardiac abnormality	53	4	25	10	1 AS aneurysm 8 RWMA 2 vegetations 14 confirmed valve lesions

*Excluding left ventricular hypertrophy.
R-to-L, right-to-left. See footnote to table 1 for other abbreviations.

fibrillation. Left ventricular hypertrophy was shown in two patients with hypertension. A large left atrium was detected in three patients in chronic fibrillation, all of whom had spontaneous contrast echoes. A regional wall motion abnormality was detected in two patients with recent Q wave infarction; both were in atrial fibrillation. The foramen ovale was patent in three patients and in one an atrial septal defect was detected.

PATIENTS WITH OTHER RISK FACTORS

Other risk factors included migraine, polycythaemia, sarcoid, connective tissue disorders, atrioventricular conduction disease, aortic valve endocarditis, and in three patients there was evidence of vascular disease from a history of angina or intermittent claudication (none of them had carotid bruits). Two patients had mild concentric left ventricular hypertrophy, although there was no history of hypertension. A large left atrium with spontaneous contrast echoes was found in the patient with sinoatrial/atrioventricular conduction disease (who had a right ventricular pacemaker). Transoesophageal echocardiography showed echoes consistent with vegetations in the patient with aortic valve endocarditis. Four of these patients had a patent foramen ovale.

PATIENTS WITHOUT RISK FACTORS

There were 41 patients with none of the risk factors described. Five were shown to have mitral valve prolapse and a bicuspid aortic valve was confirmed in another. A regional wall motion abnormality was detected in an elderly patient with no evidence of previous infarction. Eleven of these patients had a patent foramen ovale, the right-to-left shunts being detected only by the precordial studies in four. One patient had a pulmonary arteriovenous fistula and one had mitral annular calcification.

PATIENTS WITH AND WITHOUT CLINICALLY DETECTED CARDIAC ABNORMALITIES

The patients were separated into those with clinically detected cardiac abnormalities and those with no evidence of cardiac abnormality. For this purpose patients with hypertension alone as a risk factor were classified as having no cardiac abnormality irrespective of the electrocardiographic criteria of left ventricular hypertrophy (table 2).

Discussion

The discrepancy in the number of patients who have a focal ischaemic neurological event as a consequence of a cerebral embolus between clinical and necropsy studies suggests, in part, that cardiac sources of emboli often go undetected.[1–5] In a study of patients with a fatal event, it was estimated that only about 60% of patients who had a cardioembolic event would have been identified by clinical criteria alone (history of cardiac disease, atrial fibrillation, or auscultatory abnormalities), and that there would have been a 20% false positive rate and a 19% false negative rate.[20] M mode and cross sectional echocardiography have clearly improved the detection of cardiac abnormalities that are associated with embolic events[6–8] but several groups have pointed out that the yield is low in those without abnormal clinical signs.[21–23]

There is no doubt that the transoesophageal echocardiographic technique enhances our ability to detect cardiac abnormalities in patients with focal neurological events. Another advantage is that good quality images can be obtained in virtually all patients. However, many of the criticisms of precordial echocardiographic studies in these patients also apply to the transoesophageal technique. In particular, many of the abnormalities that are detected have been identified or suspected from previous clinical evaluation. In addition, the finding of a cardiac abnormality does not prove a pathogenic mechanism for the neurological event.

Cerebrovascular events are most common in the elderly, and in this group both cerebral and cardiac pathologies coexist. Clinical decisions, especially those about treatment, must take into account the probability of events based on a knowledge of the pathologies most commonly associated with them. Age is the most important risk factor for stroke, with hypertension being the second most important.[24] These statements take account of the relative risk attached to a risk factor and the attributable risk based on the frequency of the risk factor in the general population.[25] The highest relative risk for stroke is associated with rheumatic mitral valve disease and atrial fibrillation, but this combination is uncommon in the general population; overall less than 2% of all strokes are related to this pathology.[26] Moreover, atrial fibrillation itself carries only a small relative risk.[27] It is interesting that about 10% of patients with primary intracerebral haemorrhage or lacunar infarction (neither of which are due to thromboembolism) are in atrial fibrillation on presentation.[28] Moreover, there seems to be relatively little if any excess risk of recurrent stroke in patients in atrial fibrillation at the time of the presenting event compared with those in sinus rhythm.[28]

The patients investigated in this study may not reflect the general population of patients presenting with focal ischaemic neurological events, because the referral for echocardiography may have been biased by the detection of cardiac abnormalities. However, most of the patients were investigated as part of a continuing study to which all patients with a stroke or a transient ischaemic attack are referred: thus the patients cover a wide range of those presenting with such events. Although many patients with retinal arterial events have these as a consequence of cerebrovascular disease we included such patients in this study because the sources of embolism for these events have not been fully categorised. Patients in this study did not routinely undergo carotid duplex studies, mainly because of lack of the appropriate facilities and expertise at our centre during the period of this study. Thus the four patients who were studied were referred to another centre because they had carotid bruits. The role of such studies in patients with neurological events who either have no obvious risk factor for the event or who have a clinically obvious factor (such as mitral stenosis) remains to be determined.

Although the patient selection must be considered our data accord with the fact that patients with hypertension or overt cerebrovascular disease as the sole identifiable risk factor and patients with no clinically apparent cardiac disease have a relatively low yield of cardiac abnormalities on full echocardiographic evaluation. However, two causes in particular that are not detected clinically are mitral valve prolapse and a patent foramen ovale, particularly the latter. The potential for right-to-left shunting in these patients, especially if young and without other obvious risk factors, is becoming increasingly recognised.[29-31] In Lechat *et al's* study there was an association between mitral valve prolapse and the presence of a patent foramen ovale, and after the presence of a patent foramen ovale had been controlled for, mitral valve prolapse no longer correlated with stroke.[31] Although mitral valve prolapse has been associated with embolic events, clinically silent mitral valve prolapse seems to be benign, and it is therefore inappropriate to attribute a cerebral event to this finding.[32] In addition, the difficulties in diagnosing mitral valve prolapse from single plane transoesophageal studies have not yet been fully addressed. Moreover, for both mitral prolapse and a patent foramen ovale, there is no convincing evidence that any specific treatment can reduce the likelihood of recurrent events. Thus until more data are available the detection of these abnormalities may not be clinically useful. This also applies to mitral annular calcification, detected in one patient in this study. Although believed by some to be associated with thromboembolic events,[33] there is no convincing evidence of this.

For the group of patients with a clinically detected cardiac lesion it could be argued that echocardiography, whether precordial or transoesophageal, simply confirms the diagnosis. For patients in atrial fibrillation, we expect to find a large left atrium and evidence of flow abnormalities or thrombus. Thus we should not be surprised that the precordial echocardiogram shows an enlarged left atrium. The fact that no flow abnormalities are shown in the left atrium by the precordial technique relates to problems with resolution. Transoesophageal echocardiography is useful in these patients because (*a*) the transducer can be placed directly behind the left atrium and (*b*) a 5 MHz transducer is used. Evidence of flow abnormalities can be detected either as echoes consistent with thrombus[14-17] or as spontaneous contrast echoes.[34-36] Whether this information is useful or not remains debatable. Given, however, the epidemiological data that demonstrate an overall small relative risk of atrial fibrillation in stroke, it may be that the detection of these spontaneous contrast echoes provides strong evidence relating the arrhythmia to the cerebral event. Patients with these echoes, showed convincingly with transoesophageal echocardiography may benefit from anticoagulation.[37 38] This needs to be studied further.

In conclusion, transoesophageal echocardiography detects more cardiac abnormalities in patients with focal ischaemic cerebral events than precordial echocardiography. However, many of the abnormalities detected will have been predicted from previous clinical assessment of the patient. The yield in patients with no clinically detectable cardiac lesion remains relatively low. Abnormalities that are not suspected include mitral valve prolapse, which is probably not related to the cerebral event in such cases, and the possibility of right-to-left shunting. Although there is growing evidence that such shunting may have a pathogenic role in such patients, at present there are no data demonstrating that recurrences can be reduced or avoided with specific treatments. Until such data are available, echocardiography, whether precordial or transoesophageal, has a limited role in patients with focal ischaemic cerebral events.

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1 Carter AB. The immediate treatment of cerebral embolism. *Q J Med* 1957;26:335–48.

2 Groch SN, McDevitt E, Wright IS. A long-term study of cerebral vascular disease. *Ann Intern Med* 1961;55: 358–67.

3 Sherman DG, Dyken ML, Fisher M, Harrison MJG, Hart RG. Cerebral embolism. *Chest* 1986;89(suppl 3): 82S–98S.

4 Torvik A, Jorgensen L. Thrombotic and embolic occlusions of the carotid arteries in an autopsy material. 1. Prevalence, location and associated diseases. *J Neurol Sci* 1964;1:24–39.

5 Blackwood W, Hallpike JF, Kocen RS, Mair WGP.

Atheromatous disease of the carotid arterial system and embolism from the heart in cerebral infarction: a morbid anatomical study. *Brain* 1969;92:897–910.
6 Ports TA, Cogan J, Schiller NB, Rapaport E. Echocardiography of left ventricular masses. *Circulation* 1978; 58:528–36.
7 Asinger RW, Mikell FL, Sharma B, Hodges M. Observations on detecting left ventricular thrombus with two-dimensional echocardiography: emphasis on avoidance of false positive diagnoses. *Am J Cardiol* 1981;47:145–56.
8 Donaldson RM, Emanuel RW, Earl CJ. The role of two-dimensional echocardiography in the detection of potentially embolic intracardiac masses in patients with cerebral ischaemia. *J Neurol Neurosurg Psychiatry* 1981;44:803–9.
9 Frazin L, Talano JV, Stephanides L, Loeb HS, Kopel L, Gunnar RM. Esophageal echocardiography. *Circulation* 1976;54:102–8.
10 Schluter M, Hinrichs A, Thier W, Kremer P, Schroder S, Cahalan MK, *et al.* Transesophageal two-dimensional echocardiography: comparison of ultrasonic and anatomic sections. *Am J Cardiol* 1984;53:1173–8.
11 Seward JB, Khanderia BK, Oh JK, Abel MD, Hughes RW Jr, Edwards WD, *et al.* Transesophageal echocardiography: technique, anatomic correlations, implementation and clinical applications. *Mayo Clin Proc* 1988;63:649–80.
12 Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleja HB. Two-dimensional echocardiographic diagnosis of left atrial thrombus in rheumatic heart disease. A clinicopathologic study. *Circulation* 1983;67:341–7.
13 Bansal RC, Heywood JT, Applegate PM, Jutzy KR. Detection of left atrial thrombi by two-dimensional echocardiography and surgical correlation in 148 patients with mitral valve disease. *Am J Cardiol* 1989;64:243–6.
14 Ashenberg W, Schluter M, Kremer P, Schroder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986;7:163–6.
15 Zenker G, Erbel R, Kramer G, Mohr-Kahaly S, Drexler M, Harnoncourt K, *et al.* Transesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. *Stroke* 1988;19:345–8.
16 Daniel WG, Angermann C, Engberding R, Erbel R, Hanrath P, Iliceto S, *et al.* Transesophageal echocardiography in patients with cerebral ischemic events and arterial embolism—a European Multicenter Study [abstract]. *Circulation* 1989;80(suppl II):473.
17 Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JRTC. Transesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. *Stroke* 1990;21:560–5.
18 Perloff JK, Child JS, Edwards JE. New guidelines for the clinical diagnosis of mitral valve prolapse. *Am J Cardiol* 1986;57:1124–9.
19 de Belder MA, Leech G, Camm AJ. Transesophageal echocardiography in unsedated patients: technique and patient tolerance. *J Am Soc Echocardiogr* 1989;2:375–9.
20 Humphrey PRD, Harrison MJG. How often can an embolic stroke be diagnosed clinically? A clinicopathological correlation. *Postgrad Med J* 1985;61:1039–42.
21 Lovett JL, Sandok BA, Giuliani ER, Nasser FN. Two-dimensional echocardiography in patients with focal cerebral ischemia. *Ann Intern Med* 1981;95:1–4.
22 Knopman DS, Anderson DC, Asinger RW, Greenland P, Mikell F, Good DC. Indications for echocardiography in patients with ischemic stroke. *Neurology* 1982;32: 1005–11.
23 Burnett PJ, Milne JR, Greenwood R, Giles MR, Camm J. The role of echocardiography in the investigation of focal cerebral ischaemia. *Postgrad Med J* 1984;60:116–9.
24 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke and coronary heart disease. Part 1: effects of prolonged differences in blood pressure—evidence from nine prospective epidemiological studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–74.
25 Sandercock P. Risk factors for stroke: analytical epidemiology. *Cardiology in Practice* 1990;8:10–4.
26 Sandercock P, Warlow CP, Starkey IR, Jones LN. Factors predisposing to cerebral infarction; the Oxfordshire Community Stroke Project. *BMJ* 1989;298:75–80.
27 Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup DM, *et al.* The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med* 1987;317:669–74.
28 Sandercock P, Bamford J, Dennis M, Warlow CP, Jones LN, Burn J. Atrial fibrillation and stroke: prevalence, clinical features and effect on outcome in the Oxfordshire Community Stroke Project. *J Neurol* 1990;237:143–4.
29 Harvey JR, Teague SM, Anderson JL, Voyles WF, Thadani U. Clinically silent atrial septal defects with evidence for cerebral embolization. *Ann Intern Med* 1986;105:695–7.
30 Webster MWI, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, *et al.* Patent foramen ovale in young stroke patients. *Lancet* 1988;ii:11–2.
31 Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, *et al.* Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148–52.
32 Nishimura RA, McGoon MD, Shub C, Miller FA, Ilstrup DM, Tajik AJ. Echocardiographically documented mitral-valve prolapse. Long-term follow-up of 237 patients. *N Engl J Med* 1985;313:1305–9.
33 de Bono DP, Warlow CP. Mitral-annulus calcification and cerebral or retinal ischaemia. *Lancet* 1979;ii:383–5.
34 Mikell FL, Asinger RW, Elsperger KJ, Anderson WR, Hodges M. Regional stasis of blood in the dysfunctional left ventricle: echocardiographic detection and differentiation from early thrombosis. *Circulation* 1982;66:755–63.
35 Beppu S, Nimura Y, Sakakibara H, Nagata S, Park Y-D, Izumi S. Smoke-like echo in the left atrial cavity in mitral valve disease: its features and significance. *J Am Coll Cardiol* 1985;6:744–9.
36 Daniel WG, Nellessen U, Schroder E, Nonnast-Daniel B, Bednarski P, Nikutta P, *et al.* Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. *J Am Coll Cardiol* 1988; 11:1204–11.
37 Petersen P, Godtfredsen J, Boysen G, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. *Lancet* 1989;i:175–8.
38 Stroke Prevention in Atrial Fibrillation Study Group Investigators. Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. *N Engl J Med* 1990;322: 863–8.

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Variable patterns of ST-T abnormalities in patients with left ventricular hypertrophy and normal coronary arteries

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Abstract

***Background*—Classically, the ST-T configuration in the electrocardiogram of patients with left ventricular hypertrophy is said to have a typical pattern of ST depression together with asymmetrical T wave inversion (the so-called left ventricular strain pattern). However, many patients with left ventricular hypertrophy may also have ischaemic heart disease. To revise the electrocardiographic criteria for left ventricular hypertrophy the ST-T configuration in patients with left ventricular hypertrophy documented by echocardiography and with normal coronary arteries was assessed.**

***Methods*—24 patients were selected for this study. All had left ventricular hypertrophy documented by echocardiography, normal coronary arteries by cardiac catheterisation, and ST and/or T wave abnormalities in the lateral leads of their electrocardiogram. There were eight patients with aortic valve disease and 16 with hypertension who had coronary angiography as part of an investigation into the risk factors of sudden cardiac death caused by hypertensive left ventricular hypertrophy. No patient was receiving digitalis preparations or had electrolyte disturbances, and none had a previous myocardial infarction or ventricular conduction defect.**

***Results*—Typical electrocardiographic evidence of left ventricular strain was found in approximately two thirds (63%) of patients and 95% of this subgroup had asymmetrical T wave inversion. Flat ST segment depression, with or without T wave inversion or isolated T wave inversion (symmetrical or asymmetrical) in the anterolateral leads, was seen in the remaining 37% of patients.**

***Conclusions*—These findings indicate that left ventricular hypertrophy without coronary artery disease can cause variable types of ST-T abnormalities in the anterolateral leads including the typical left ventricular strain pattern and non-specific ST-T changes. Non-specific abnormalities could not be distinguished from those of coronary artery disease and may adversely affect the accuracy of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy because they do not accord with the criteria for left ventricular strain.**

Carter and Estes showed that electrocardiographic evidence of left ventricular strain defined as asymmetrical ST depression and T wave inversion in the anterolateral leads (I, aVL, V5 and/or V6) correlated significantly with left ventricular weight at necropsy.[1] Left ventricular strain (ST segment depression $\leq 0\cdot 1$ mV with asymmetrical T wave inversion) in the anterolateral leads was reported to be 95% specific for left ventricular hypertrophy in the absence of digitalis treatment.[2] However, in clinical practice, it is not uncommon to find that some patients, who have electrocardiographic left ventricular hypertrophy confirmed by echocardiography, have symmetrical or asymmetrical T wave inversion without ST segment depression. It is not certain whether such T wave changes without ST-segment depression occur because of left ventricular hypertrophy itself or on account of associated coronary artery disease particularly as it is well established that patients with electrocardiographic left ventricular hypertrophy and ST-T abnormalities are eight times more likely to have coronary artery disease than those who have electrocardiographic left ventricular hypertrophy without repolarisation wave abnormalities.[3] For this reason, we decided to review the patterns of repolarisation wave abnormalities in a group of patients with left ventricular hypertrophy documented by echocardiography, ST and/or T wave abnormalities on their scalar electrocardiograms and with normal coronary arteries demonstrated by coronary angiography.

Patients and methods

Patients were selected for this study if they had normal coronary arteries and left ventricular hypertrophy documented by echocardiography. Their electrocardiograms also had to show ST and/or T wave abnormalities in the lateral leads. Eight patients had aortic valve disease (aortic stenosis and/or regurgitation) with or without chest pain suggestive of angina pectoris and had left heart catheterisation and coronary angiography as a part of their general assessment for aortic valve replacement. Sixteen patients had hypertension and they had coronary angiography as a part of an ongoing study investigating the risk factors of sudden cardiac death in hypertensive left ventricular hypertrophy.[4] No patient had a previous myocardial infarction, intraventricular conduction defect, or was being treated with digitalis. Myocardial infarction was excluded in these patients on the basis of clinical history and contrast left ventriculography.

The electrocardiograms were recorded with either a Mingorec 4 electrocardiograph (Siemens-Elema) or a computer compatible electrocardiograph developed locally.[5] ST segment depression was regarded as present when depression ≤0·1 mV occurred 40 ms after the J point. The configuration of the ST-T changes was classified according to the following rules:

ST segment depression—downward sloping, flat or upward sloping.

T wave inversion—symmetrical, or asymmetrical with or without terminal overshoot.

The echocardiograms were recorded with a Diasonics Cardiovue 3400 Phased Array imaging system and a 2·5 MHz transducer. Patients were positioned semisupine in the 45° left lateral position and the echo windows that best demonstrated the septal and posterior walls of the left ventricle were chosen in the 3rd, 4th, or 5th left parasternal area. M mode recordings were obtained and measurements were made of the interventricular septum, posterior wall of the left ventricle, and the left ventricular internal dimension at the tip of the mitral valve at end diastole according to the Penn Convention.[6] The left ventricular masses were calculated by the formula of Devereux and Reichek[6] as follows:

$$\text{LVM} = 1{\cdot}04[(\text{IVS} + \text{PWLV} + \text{LVIDD})^3 - (\text{LVIDD})^3] - 13{\cdot}6\text{g}$$

where LVM is the left ventricular mass (g), IVS is the interventricular septum (cm), PWLV is the posterior wall of left ventricle (cm), and LVIDD is the left ventricular internal dimension (cm) at end diastole. The masses were indexed to the body surface area, the latter being obtained from the following equation[7]:

$$\text{BSA} = 0{\cdot}0001 \times 71{\cdot}84 \times \text{Wt}^{0{\cdot}425} \times \text{Ht}^{0{\cdot}725}$$

where BSA is the body surface area (m^2), weight (Wt) (kg), and height (Ht) (cm).

Echocardiographic left ventricular hypertrophy was diagnosed when the left ventricular mass index exceeded 131 g/m^2 and 108 g/m^2 in men and women respectively.[8] Absence of coronary artery disease was defined as absolutely normal coronary arteries.

Results

Twenty four patients completed the study (18 men and six women, mean (SD) age 53·2 (10·46) years, range 31–72 years). All had echocardiographic left ventricular hypertrophy and their left ventricular mass indexed to body surface area ranged from 137 to 307 g/m^2 with a mean (SD) of 189·34 (53·7) g/m^2. Left ventricular hypertrophy was caused by hypertension in 16/24 (66%) and aortic valve disease (aortic stenosis and/or regurgitation) in 8/24 (34%) of the patients. All had absolutely normal coronary arteries. The table shows their left ventricular mass indexed to body surface area (g/m^2), QRS axes, and pattern of ST segment depression and T wave inversion.

Asymmetrical ST-segment depression that was bowed upward in the anterolateral leads was seen in 15/24 (63%) of the patients. All had T wave inversions in the anterolateral leads except one patient who had diphasic T waves in leads I, V5, and V6 (fig 1). The T wave inversion (≤0·1 mV) in the anterolateral leads of the other 14/24 (58%) patients was predominantly asymmetrical as shown in fig 2.

Flat ST segment depression in the anterolateral lead was found in 5/24 (21%) of the patients (fig 3). The associated T wave changes in the patients included asymmetrical T wave inversion in two patients, flat T wave in

Electrocardiographic findings in 24 patients with an increase in indexed left ventricular mass

No	Sex	Age (y)	LVMI (g/m²)	Diag	ECG LVH	ST segment depression	T wave inversion	QRS axis
1	M	58	169·6	HBP	–	1, aVL, V6*	I, aVL, V5, V6†	30
2	F	52	127·8	"	+	I, aVL, V2–V6*	I, aVL, V2–V6†	12
3	M	45	162·3	"	–	None	I, aVL, V5, V6†	16
4	F	38	193	"	–	I, aVL, V5, V6*	I, aVL, V5, V6†	43
5	M	53	145	"	–	V5, V6 (flat)	aVL (flat)	35
6	M	31	137	"	+	I, aVL, V3–V6*	I, aVL, V4–V6,† V3 (symmetrical)	28
7	M	63	180·1	"	–	I, V5, V6*	aVL (flat)	66
8	M	62	216·0	"	+	None	I, aVL, V6 (symmetrical)	36
9	M	39	144	"	–	I, aVL, V5, V6*	I, aVL†	03
10	M	55	245	"	–	None	aVL†	−05
11	M	53	145	"	+	aVL (flat)	aVL†	17
12	F	46	126·1	"	+	V5 (flat)	aVL (flat)	67
13	F	53	140	"	–	V5, V6 (flat)	I, aVL, V5, V6†	−07
14	M	54	193·3	"	+	aVL*	I, aVL, V5, V6†	25
15	M	52	193	"	–	I, aVL, V5, V6*	I, aVL, V5, V6†	14
16	F	54	305	"	+	I, aVL, V5–V6*	I, aVL, V5, V6†	01
17	M	56	220	AVD	+	I, aVL, V4–V6*	I, III, aVL, V4–V6†	−01
18	M	36	155	"	–	None	I, II, III, aVL, aVF†, V5, V6	42
19	M	72	197	"	+	I, aVL, aVF, V3–V6*	I, aVL, AVF, V3–V6†	04
20	M	56	246	"	+	I, II, aVL, aVF, V5, V6 (flat)	I, II, aVF, V5, V6†, aVL (symmetrical)	15
21	M	69	307	"	+	I, II, III, aVF, V5, V6*	I, II, III, aVL, aVF, V5, V6†	46
22	M	75	137	"	+	I, aVL, V3–V6*	I, II, aVL, V3–V6†	64
23	F	52	274	"	+	I, II, aVL, V5, V6*	I, II, aVL, V5, V6†	18
24	M	63	186	"	+	I, II, III, aVL, aVF, V5, V6*	I, II, III, aVL, aVF, V5, V6†	−16

*Downward sloping ST depression (≤0·1 mV). 40 ms after the J point.
†Asymmetrical T wave inversion with terminal overshoot.
HBP, high blood pressure; AVD, aortic valve disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy.

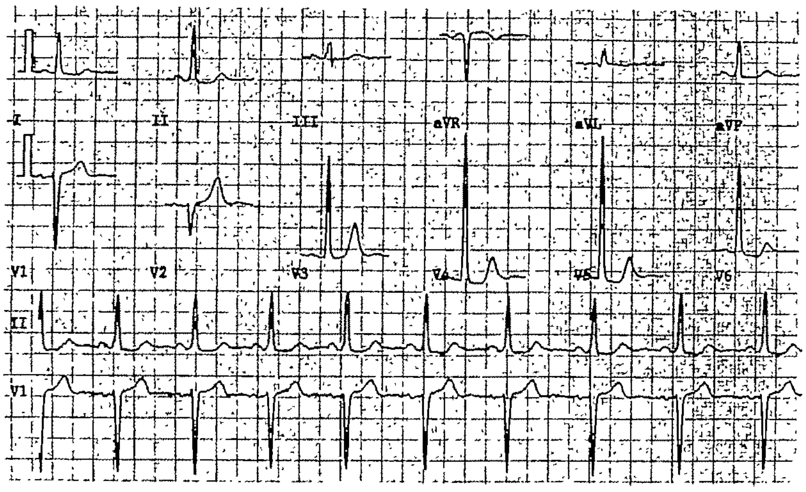

Figure 1 ST depression and diphasic T waves in I, V5, V6 in a 53 year old man with hypertension and normal coronary arteries. His echocardiographic left ventricular mass was 145 g/m².

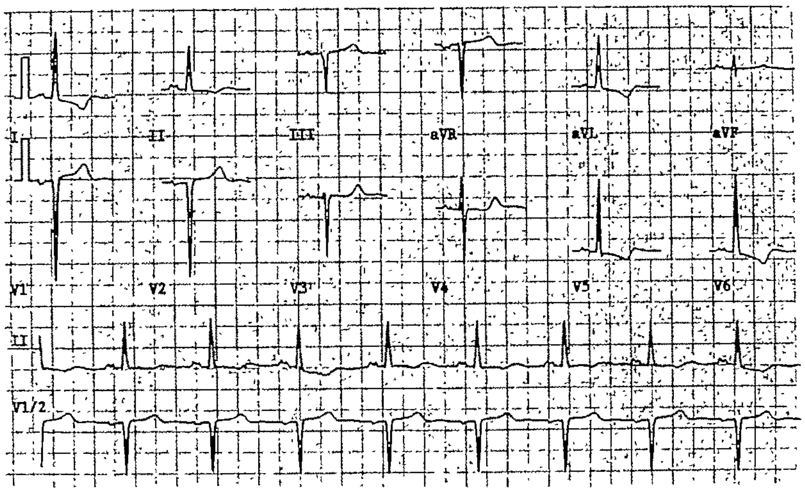

Figure 2 Electrocardiogram of a 52 year old woman with aortic valve disease and normal coronary arteries. Her echocardiographic left ventricular mass was 274 g/m². The electrocardiogram shows typical left ventricular strain with bowing upwards and sloping down into an inverted T wave with terminal overshoot in the anterolateral leads.

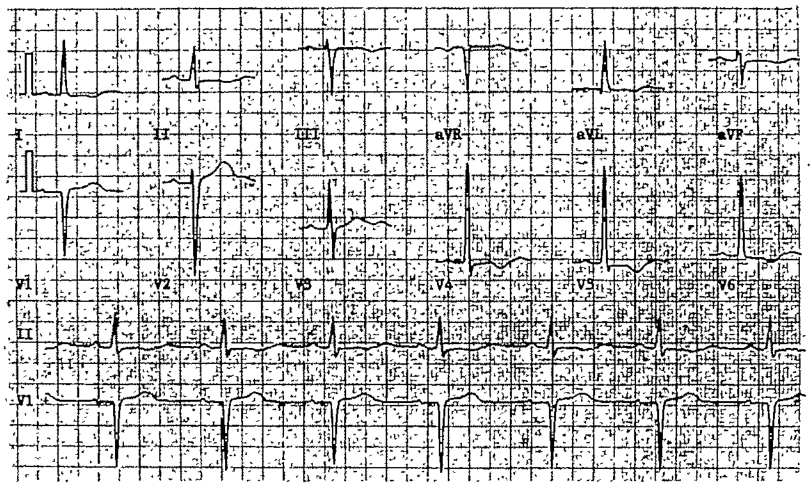

Figure 3 Flat ST segment depression in left ventricular hypertrophy without coronary artery disease in a 53 year old woman with hypertension. Her echocardiographic left ventricular mass was 140 g/m². The electrocardiogram shows T wave inversion in the anterolateral leads with flat ST segment depression.

two other patients, and symmetrical T wave inversion in one patient.

There were isolated T wave changes ($\leq$0·00 mV) without ST depression in the anterolateral leads in 4/24 (16%) of the patients: three (12%) patients with asymmetrical T wave inversion (fig 4) and one (4%) with mainly symmetrical T wave inversion in leads V5 and V6 (figure 5).

Discussion

The generally accepted definition of left ventricular strain is an ST segment depression that is bowed upward and slopes down into an inverted asymmetrical T wave,[9] a concept that was introduced by Rykert and Hepburn.[10] Beach *et al* suggested that the repolarisation wave abnormalities of left ventricular hypertrophy without coronary artery disease could often be distinguished from those of coronary artery disease by the presence of one or more of the following five features: depression of the J point, asymmetry of the T wave with rapid return to the baseline, terminal positivity of the T wave (overshoot), T wave inversion in V6 greater than 0·3 mV, and T wave inversion greater in V6 than in V4.[11] However, it is not rare in clinical practice to see ST-T abnormalities associated with left ventricular hypertrophy that do not fulfil these criteria of left ventricular strain and thus may be confused with those of coronary artery disease. The latter issue is further complicated by the fact that patients with left ventricular hypertrophy and ST-T abnormalities are more at risk of coronary artery disease than those who do not have abnormal repolarisation.[3]

In this study 15/24 (63%) of the patients had asymmetrical ST segment depression (convex upward and sloping downwards) and 14/15 (95%) of these patients had asymmetrical T wave inversion. However, flat ST segment depression with asymmetrical T wave inversion was observed in other (5/24, 21%) patients with left ventricular hypertrophy and normal coronary arteries. Furthermore, isolated T wave changes (asymmetrical or symmetrical inversion) were seen in four of the 24—that is, 16% of the repolarisation wave abnormalities associated with left ventricular hypertrophy and normal coronary arteries.

The mechanism for these ST-T abnormalities that do not accord with the definition of left ventricular strain is difficult to explain but it is well established that myocardial ischaemia may present on the surface electrocardiogram as flat ST segment depression, flat T waves, symmetrical T inversion, or non-specific ST-T abnormalities.[12] None of these patients was taking digitalis or had electrolyte disturbances to account for the ST-T changes. Furthermore, the absolutely normal coronary arteries, documented by coronary angiography, exclude coronary artery disease as a possible explanation. However, left ventricular hypertrophy with normal coronary arteries is a known cause of angina pectoris presumed to be due to an abnormal coronary reserve which leads to relative coronary insufficiency.[13] Therefore, the most likely explanation for flat ST segment

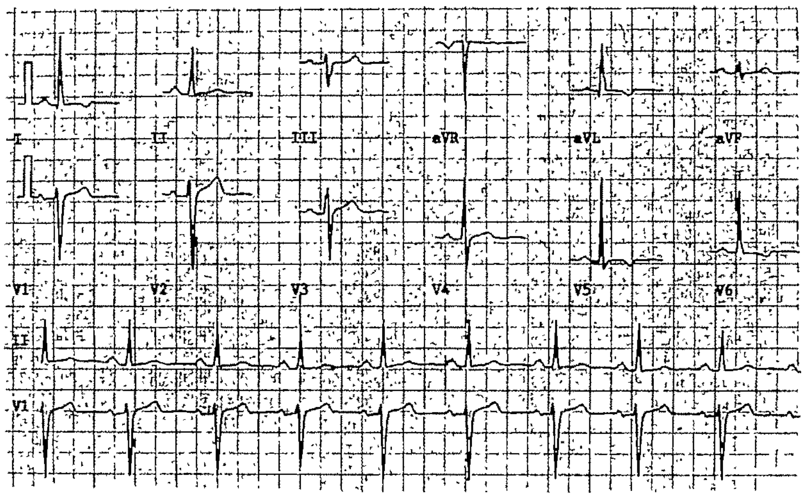

Figure 4 Electrocardiogram of a 45 year old man with left ventricular hypertrophy caused by hypertension (echocardiographic left ventricular mass of 162·3 g/m²). It shows mainly asymmetrical T wave inversion in the anterolateral leads without ST depression.

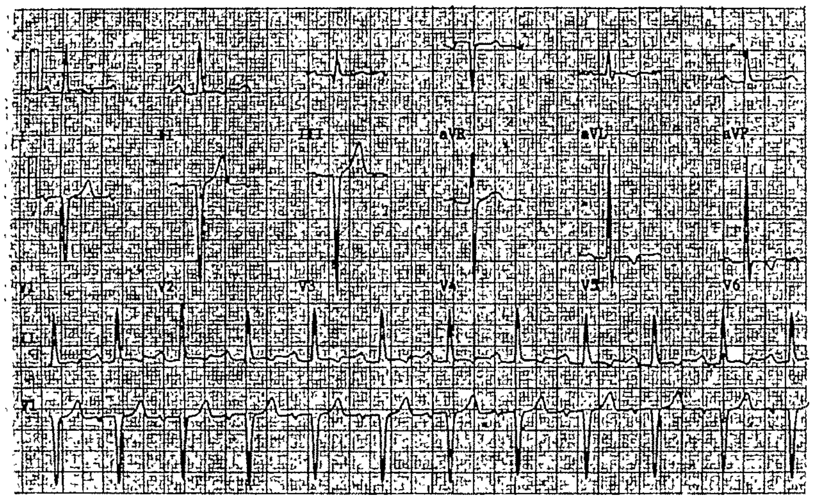

Figure 5 Electrocardiogram of a 36 year old man with mixed aortic valve disease and normal coronary arteries. It shows T wave inversion without significant ST segment depression in the anterolateral leads. His echocardiographic left ventricular mass was 155 g/m².

depression or isolated T wave changes in patients with left ventricular hypertrophy and normal coronary arteries is probable latent myocardial ischaemia or a variant of left ventricular strain. However, we cannot rule out a structural abnormality in the myocardium, such as interstitial fibrosis, as a cause of primary non-specific ST-T abnormalities in these patients with left ventricular hypertrophy and normal coronary arteries.

We conclude that typical left ventricular strain defined as asymmetrical ST segment depression ($\leq 0 \cdot 1$ mV, 40 ms after the J point) with T wave inversion occurs in approximately two thirds of patients with left ventricular hypertrophy and normal coronary arteries, with T wave inversion being asymmetrical in 95% of these patients and that flat ST segment depression with or without T wave inversion, and isolated T wave changes can be produced by left ventricular hypertrophy without coronary artery disease.

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1 Carter WA, Estes EH. Electrocardiographic manifestations of ventricular hypertrophy: a computer study of ECG-anatomic correlations in 319 cases. *Am Heart J* 1964; 68:173–82.

2 Devereux RB, Reichek N. Repolarisation abnormalities of left ventricular hypertrophy. Clinical, echocardiographic and haemodynamic correlates. *J Electrocardiol.* 1982; 15:47–54.

3 Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary artery disease. *Ann Intern Med* 1970;72:813–22.

4 Pringle SD, Macfarlane PW, McKillop JH, Lorimer AR, Dunn FG. Pathophysiologic assessment of left ventricular hypertrophy and strain in asymptomatic patients with essential hypertension. *J Am Coll Cardiol* 1989;13: 1377–81.

5 Watts MP, Shoat DB. Trends in electrocardiograph design. *J IERE* 1987;57:140–50.

6 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. *Circulation* 1977;55:613–8.

7 DuBois D, DuBois EF. A formula to estimate approximate surface area if height and weight be known. *Arch Intern Med* 1916;17:863–71.

8 Devereux RB, Lutas EM, Casale PN. Standardisation of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 1984;4:1222–30.

9 Milliken JA, Macfarlane PW, Lawrie TDV. Enlargement and hypertrophy. In: Macfarlane PW, Lawrie TDV, eds. *Comprehensive electrocardiology.* Oxford: Pergamon, 1989:631–70.

10 Rykert HE, Hepburn J. Electrocardiographic abnormalities characteristic of certain cases of arterial hypertension. *Am Heart J* 1935;10:942–54.

11 Beach C, Kenmure ACF, Short D. Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia. *Br Heart J* 1981;46:285–9.

12 Chou CT. Myocardial infarction, injury and ischemia. In: *Electrocardiography in clinical practice.* 2nd ed. Orlando: Grune and Stratton, 1986:147–225.

13 Cannon RO, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and normal coronary arteries—role of small coronary arteries. *Am J Cardiol* 1985;55:50B–60B.

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Negative extrathoracic pressure ventilation for phrenic nerve palsy after paediatric cardiac surgery

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Abstract

***Objective*—To investigate the feasibility of negative extrathoracic pressure ventilation as a respiratory support following phrenic nerve palsy after cardiac surgery.**

***Design*—An uncontrolled pilot study.**

***Patients*—14 patients aged one week to 30 months (median 5·3 months) with phrenic nerve palsy diagnosed by phrenic nerve conduction tests and diaphragmatic electromyograms. Four had bilateral and 10 unilateral palsy. Before treatment all required oxygen and 10 were receiving positive pressure ventilation. One of the patients with bilateral and four of the patients with unilateral palsies had undergone a plication before negative pressure ventilation was started.**

***Intervention*—Treatment was started 6–65 days (median 23) after operation with a newly designed system which included a Perspex chamber, which gave easy access to the child, and an elastic latex neck seal. Continuous negative pressure was used in conjunction with intermittent positive pressure ventilation while continuous or intermittent negative pressure ventilation was used in extubated infants.**

***Results*—All four patients with bilateral palsy survived with long-term intermittent negative pressure ventilation and did not require further surgery. Of the 10 with unilateral lesions, seven required no further surgery, two underwent plication, and one had a re-plication. Three patients with unilateral palsy died of non-respiratory causes. The duration of positive pressure ventilation after starting negative pressure ranged from 0 to 23 days (median 6). Treatment with negative pressure lasted for 3–241 days (median 32) and was predominantly administered off the intensive care unit, including at home.**

***Conclusions*—Negative pressure ventilation may be an alternative to positive airway pressure ventilation in the management of phrenic nerve palsy. A multicentre randomised controlled trial is now required to assess further the role of negative pressure ventilation in phrenic nerve palsy.**

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Phrenic nerve palsy is a complication of surgery for congenital heart disease[1] that can cause respiratory failure and necessitate prolonged ventilation via an endotracheal tube or a tracheostomy.[2] These techniques contribute to the development of infections of the lower respiratory tract, often in the atelectatic lung adjacent to the paralysed diaphragm, thus further prolonging the need for respiratory support. The younger the child the more marked the respiratory compromise. This is due to the infant's greater reliance on the diaphragm for breathing in the presence of a relatively horizontal rib cage, a compliant chest wall, and a recumbent posture.[3-5] Treatment of phrenic nerve palsy is initially conservative but if the patient cannot be weaned from positive airway pressure ventilation or has a persistent oxygen requirement, diaphragmatic plication is usually performed.[1] However, this surgical procedure does not always ameliorate the respiratory failure, which may require treatment for weeks or months even in patients in whom the nerve injury is temporary.

We report our findings in 14 patients with phrenic nerve palsy, some of whom had undergone diaphragmatic plication. Negative extrathoracic pressure ventilation was used with the aim of providing respiratory support without the need for a plication or replication, long-term endotracheal intubation, or tracheostomy.

Patients and methods

PATIENTS

The table shows the clinical details of the 14 patients with phrenic nerve palsy who were treated with negative extrathoracic pressure ventilation between July 1987 and March 1990. In all patients the diagnosis of phrenic nerve palsy was based on the observation of paradoxical abdominal movement during spontaneous respiration, fluoroscopic and/or ultrasonic findings of an elevated raised hemi-diaphragm with paradoxical movement on spontaneous breathing, and impaired phrenic nerve latencies and diaphragmatic electromyograms. Before treatment with negative pressure, all 14 patients were receiving oxygen and 10 were receiving intermittent positive pressure ventilation. The four infants who were breathing spontaneously had been weaned off positive airway pressure respiratory support 1–7 days (median 1) before negative pressure treatment was started.

Table 1 Patient details before and after the start of ventilation by negative extrathoracic pressure (VNEP)

Patient No	*Diagnosis*	*Surgery*	*Site of PNP*	*Plication*	*Duration of IPPV before VNEP (days)*	*Duration of IPPV after VNEP (days)*	*Duration of VNEP (days)*	*Plication/ replication after VNEP*	*Survival*
1	TGA, VSD, PS	Right B-T shunt	Right	Yes	22	3	9	Yes	Dead
2	TGA	Mustard's procedure	Bilateral	No	24	16	97	No	Alive
3	TGA, VSD, PS, PDA	Left B-T shunt	Left	Yes	7	0	77	No	Alive
4	TGA, PS	Right B-T shunt	Right	Yes	25	23	13	No	Dead
5	TOF	Full repair	Left	No	5	8	3	Yes	Alive
6	TGA	Senning's procedure	Bilateral	Yes	41	4	233	No	Alive
7	TOF	Full repair	Left	Yes	20	10	6	No	Dead
8	TGA, VSD, ASD, previous PA banding, ligation of PDA and repair of coarctation	Arterial switch Closure of VSD	Left	No	23	7	61	No	Alive
9	TGA	Arterial switch	Left	No	12	0	5	No	Alive
10	TGA, VSD	Mustard's procedure	Left	No	57	0	11	No	Alive
11	TGA, VSD, PDA	Arterial switch	Left	No	15	0	24	No	Alive
12	Anomalous left coronary artery	Full repair	Bilateral	No	36	7	241	No	Alive
13	TGA	Arterial switch	Bilateral	No	34	10	165	No	Alive
14	TGA, VSD, Mustard's procedure at 1 year	Relief of pulmonary venous obstruction	Right	No	18	5	40	Yes	Alive

ASD, atrial septal defect; B-T, Blalock-Taussig; PDA, patent ductus arteriosus; PNP, phrenic nerve palsy; PA, pulmonary artery; PS, pulmonary stenosis; TOF, tetralogy of Fallot; TGA, transposition of great arteries; VSD, ventricular septal defect; IPPV, intermittent positive airway pressure ventilation.

The indication for negative extrathoracic pressure ventilation was difficulty in weaning from positive pressure ventilation or, in those breathing spontaneously, a persistent or increasing oxygen requirement and respiratory distress. The timing of the start of treatment was partly dependent on the availability of equipment. Ages at the start of treatment ranged from one week to 30 months (median 5·3 months) and weight from 2·3 kg to 10 kg (median 5·3 kg). Negative pressure treatment started 6–65 days (median 23) after cardiac surgery.

METHODS

The system for applying negative extrathoracic pressure ventilation (Homer and Wells, DHB Tools) has been described in detail elsewhere.[6] In brief, it consists of a Perspex chamber that encloses the patient from below the neck. The chamber is made airtight by a latex neck seal that is placed over a polo-necked stockinet vest on the infant. Routine access was via two portholes on each side of the chamber. Foam gaskets on the inside of these portholes formed a seal round the arms enabling the negative pressure to be maintained while routine care was being administered. Emergency access could be gained by undoing two quick-release catches at the side of the chamber, thus allowing the lid of the chamber to swing upwards, to give easy and rapid access to the infant.

In intubated patients receiving positive pressure ventilation, continuous negative extrathoracic pressure was applied at pressures of − 6 to − 8 cm water. At the same time, the peak inspiratory pressure was reduced by the magnitude of the negative pressure used and the end-expiratory pressure was reduced as close as possible to zero. For example, an infant receiving peak inspiratory/end expiratory pressures of + 26/4 cm H_2O would change to + 18/0 cm H_2O immediately before a continuous negative pressure of − 8 cm H_2O was applied. If continuous negative pressure had to be stopped temporarily, the reverse pressure changes were made.

Immediately after extubation, intermittent negative pressure ventilation was started. It was also used to avoid reintubation in patients who were breathing spontaneously and had deteriorated despite continuous negative pressure. During intermittent negative pressure, peak pressures of − 30 to − 40 cm H_2O were used with end expiratory pressures of − 6 to − 8 cm H_2O. Extubated patients were gradually weaned from intermittent to continuous negative extrathoracic pressure. As the patient's condition improved the chamber was opened every 4–12 hours for feeding and parental contact and the patient spent increasingly longer times out of the chamber.

Parents were encouraged to take part in nursing their child both in and out of the chamber. When treatment was to continue at home parents were trained to use the negative pressure respiratory support system and were provided with a transcutaneous oxygen monitor (Kontron 821S, Watford) specially modified for home use.[7]

Phrenic nerve testing is a useful bedside technique for the diagnosis of nerve injury and resultant diaphragmatic palsy. The details of the technique have been described elsewhere.[8] It involves percutaneous stimulation of the phrenic nerves in the neck and recordings of the diaphragmatic compound muscle action potential as electromyograms from surface electrodes. The diagnosis of phrenic nerve injury is based on the assessment of delayed phrenic nerve latency (conduction time) or an absent diaphragmatic electromyogram despite repeated phrenic nerve stimulation.

Diaphragmatic plication was performed by standard techniques.[1 9]

Results

The table outlines the results of treatment with negative pressure. All four children with bilateral phrenic nerve palsy survived after long-term intermittent negative pressure ventilation and did not receive further surgery. After the start of negative pressure in the 10 patients with unilateral phrenic nerve palsies, seven recovered without further surgery, two had plication, and one a re-plication. One of the three patients who had a plication could not be extubated and underwent a further period of treatment with negative pressure after this operation. Plication was performed in all three cases because respiratory failure continued despite respiratory support with negative pressure.

Three of the patients with unilateral palsy died: one from candidal septicaemia, one intraoperatively during a pulmonary artery banding, and one after a cardiac arrhythmia which led to a cardiac arrest.

The length of positive pressure ventilation after the start of negative extrathoracic pressure ventilation ranged from 0 to 23 days (median 6). Treatment with negative pressure lasted from three to 241 days (median 32). The patients required intensive care for 14–99 days (median 38) and treatment in hospital for 26–186 days (median 75). Three patients with bilateral phrenic nerve palsy continued treatment at home for 93, 108, and 113 days.

There were no statistically significant differences in the total duration of respiratory support with either positive or negative pressure or between the five patients who had undergone a plication before negative pressure treatment and those who had not (Mann-Whitney U test).

Two of the 14 patients temporarily developed sore necks as a result of intermittent negative pressure treatment but in neither case did this necessitate discontinuation of the treatment. There were no other complications.

Phrenic nerve conduction studies were repeated at intervals according to the patient's respiratory state and the frequency of their outpatient attendances. These studies were useful in assisting in decisions about the duration of treatment and the prognosis. Nine of the 14 patients recovered normal phrenic nerve latency and diaphragmatic electromyograms at 1·5 to 25 months (median 15) after operation. The three patients who died showed no recovery in phrenic nerve conduction by the time of death, one patient showed no recovery 10 months postoperatively, and one was lost to follow up. Most patients showed clinical evidence of improvement before electrophysiological evidence of recovery.

At follow up, 2–22 months (median 9·5) after the end of the negative pressure treatment, the 11 surviving patients showed clinically normal respiratory function.

Discussion

Retrospective studies have reported phrenic nerve palsy in 1–2% of patients after surgery for congenital heart disease.[1 2] In a prospective study in which we used percutaneous stimulation of the nerve to confirm phrenic nerve injury, this complication was found in 10% of cases.[8] The probable reason for the underdiagnosis of phrenic nerve palsy is that many children with abnormal electrophysiological studies do not have apparent clinical manifestations. In addition, the non-specific nature of clinical signs, such as a raised hemi-diaphragm on the chest radiograph, may result in the diagnosis not being considered. The use of phrenic nerve testing and the analysis of the terminal latencies and diaphragmatic electromyograms were helpful in diagnosis and in assessing the degree of recovery.

A mortality of between 10% (three of 32 cases)[2] and 36% (four of 11 cases)[9] has been reported in children with congenital heart disease and unilateral palsies. There are no data on mortality in bilateral palsies[10] but they would probably show an even higher incidence.

The use of negative extrathoracic pressure ventilation as a form of respiratory support dates back to the last century.[11] A previous case report describes the use of this treatment in an infant with diaphragmatic paralysis after a birth injury.[12] Both positive airway pressure ventilation and continuous negative extrathoracic pressure can help to stabilise the paralysed diaphragm and thereby prevent it from encroaching on tidal volume by paradoxical motion. However, negative pressure has two advantages over positive pressure respiratory support given through an endotracheal airway. Firstly, negative pressure support is non-invasive and may obviate the need for endotracheal intubation or tracheostomy; both are techniques that increase the risk of introducing pathogens into the lung. Moreover, because diaphragmatic paralysis may impair the ability to clear secretions, the risk of infection is particularly high in intubated patients with phrenic nerve palsy. Secondly, negative pressure has important theoretical haemodynamic advantages. Positive airway pressure ventilation may decrease venous return to the right side of the heart, increase pulmonary vascular resistance, and reduce pulmonary blood flow.[13] A reduction in pulmonary blood flow may be particularly deleterious after cardiac surgery, especially when pulmonary blood flow is already compromised. The use of positive pressure ventilation in conjunction with continuous negative pressure, as outlined above, can lead to a fall in mean airway and mean intrathoracic pressures. The fall in mean intrathoracic pressure would in turn be expected to improve systemic venous return and pulmonary blood flow. However, in lesions with a left to right shunt such as a ventricular septal defect, increased pulmonary blood flow may be disadvantageous in that it might precipitate or exacerbate pulmonary oedema. This potential complication was not identified in any of our patients.

Nasal continuous positive airway pressure is less invasive than endotracheal intubation and could be considered an alternative to negative pressure treatment. However, ventilation with such a system is less practicable because the proportion of positive pressure reaching the lungs is variable and is much reduced whenever the patient's mouth opens.

The use of negative extrathoracic pressure ventilation in infants and children largely ceased in the 1970s. This was the result of advances in the application of positive airway pressure ventilation and the technical problems associated with the use of negative pressure. The latter included difficulties in obtaining an adequate neck seal and in gaining access to the patient. Having redesigned the negative pressure chamber to overcome these difficulties we have re-introduced it into paediatric practice.[6]

In this preliminary and uncontrolled study there were no strict criteria for the initiation of negative pressure treatment. Treatment was started when the cardiologist thought that the child's respiratory course was failing to improve despite standard treatment.

Of the six patients with unilateral lesions undergoing positive pressure ventilation after the initiation of negative pressure, two received a plication and one a re-plication. Two of these three plications took place when only the continuous mode of negative pressure was available; that is, before the development of intermittent negative pressure ventilation. One plication was, however, required despite the use of intermittent negative pressure ventilation. The four spontaneously breathing infants with unilateral lesions and the four infants with bilateral lesions all progressed without requiring further surgery. Thus negative pressure may have led to the avoidance of plication or re-plication in 11 of these 14 patients.

The four patients with bilateral lesions required negative pressure treatment for a prolonged period of three to nine months. Access to the infant nursed in a negative pressure chamber is more limited than that in an infant undergoing positive pressure respiratory support. Stimulation and play and consequently development could therefore be hampered in infants requiring long-term treatment. However, as lung function improved, the patient was able to be taken out of the negative pressure chamber for progressively longer periods to be cuddled, played with, and stimulated. These difficulties with access have to be balanced against the advantages of negative pressure. These include the avoidance of long-term intubation and its associated problems with infection, and the greater feasibility of using negative pressure support outside the intensive care unit and at home.

Further improvements to the negative pressure system have recently been achieved,[14] including for example the development of a port in the base of the chamber for the insertion of x ray films allowing a radiograph to be taken without disturbance to the negative pressure.

Our results suggest that negative extrathoracic pressure ventilation is an effective and practicable treatment and may be an important alternative to long-term positive airway pressure ventilation in infants and children with unilateral or bilateral phrenic nerve palsy after surgery for congenital heart disease. A randomised controlled trial is required to evaluate negative pressure ventilatory support in the treatment of phrenic nerve palsy and to assess its possible role as an alternative to positive airway pressure ventilation and to diaphragmatic plication.

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1 Langer JC, Filler RM, Coles J, Edmonds JF. Plication of the diaphragm for infants and young children with phrenic nerve palsy. *J Pediatr Surg* 1988;23:749–51.
2 Mickell JJ, Oh KS, Siewers RD, Galvis AG, Fricker FJ, Mathews RA. Clinical implications of postoperative unilateral phrenic nerve paralysis. *J Thorac Cardiovasc Surg* 1978;76:297–303.
3 Robotham JL. A physiological approach to hemidiaphragm paralysis. *Crit Care Med* 1979;7:563–6.
4 Muller NL, Bryan AC. Chest wall mechanics and respiratory muscles in infants. *Pediatr Clin North Am* 1979;**26**:503–16.
5 Bryan AC, Wohl MEB. Respiratory mechanics in children. In: Fishman AP, Macklem PT, Mead J, eds. *Handbook of physiology. Section 3: The Respiratory System*. Bethesda, Maryland: American Physiological Society, 1986:vol 3, part 1:179–91.
6 Samuels MP, Southall DP. Negative extrathoracic pressure in treatment of respiratory failure in infants and young children. *BMJ* 1989;299:1253–7.
7 Poets CF, Samuels MP, Noyes JP, Jones KA, Southall DP. Home monitoring of transcutaneous oxygen tension in the early detection of hypoxaemia in infants and young children. *Arch Dis Child* 1991;66:676–82.
8 Mok Q, Ross-Russell R, Mulvey D, Green M, Shinebourne EA. Phrenic nerve injury in infants and children undergoing cardiac surgery. *Br Heart J* 1991;65:287–92.
9 Stone KS, Brown JW, Canal DF, King H. Long term fate of the diaphragm surgically plicated during infancy and childhood. *Ann Thorac Surg* 1987;44:62–5.
10 Stewart S, Alexson C, Manning J. Bilateral phrenic nerve paralysis after the Mustard procedure: experience with four cases and recommendations for management. *J Thorac Cardiovasc Surg* 1986;92:138–41.
11 Woollam CHM. The development of apparatus for intermittent negative pressure respiration (1). 1832–1918. *Anaesthesia* 1976;31:537–47.
12 Weisman L, Woodall J, Merenstein G. Constant negative pressure in the treatment of diaphragmatic paralysis secondary to birth injury. *Birth Defects* 1976;12:297–302.
13 Tyler DC. Positive end-expiratory pressure: a review. *Crit Care Med* 1983;11:300–8.
14 Raine J, Wright TAM, Samuels MP, Southall DP, Modi N, Harvey S, *et al*. The use of continuous extrathoracic pressure in neonatal respiratory failure. In: Lafeber HN, ed. *Fetal and neonatal physiological measurements*. London: Excerpta Medica, 1991:265–70.

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Cross sectional and Doppler echocardiographic evaluation of aortopulmonary shunts

Yasunori Horiguchi, Satoshi Hiraishi, Hitoshi Misawa, Youtaro Agata, Seimei Nakae

Abstract

***Background*—Shunt vessels were imaged and shunt flow was analysed by cross sectional and Doppler echocardiography in 12 patients who had had 14 shunt procedures (nine left Blalock-Taussig shunts, three right Blalock-Taussig shunts, one modified Waterston shunt, and one central shunt).**

***Methods*—The shunt vessels were classified by echocardiography as uniformly patent, segmentally stenosed, and uniformly stenosed. These findings were compared with those of angiography. Also the peak flow velocities at the aortic and the pulmonary ends of the shunt vessels were measured by Doppler echocardiography and the ratio of these values was calculated for each shunt.**

***Results*—Twelve (85·7%) of 14 shunt vessels were imaged along their entire length by cross sectional echocardiography. The two remaining shunt vessels were only partially imaged. In 10 patients who also had angiography the echocardiographic and angiographic images of the shunt vessels were identical. The ratio of the peak flow velocity measured at the aortic and the pulmonary ends of the shunt vessel was significantly larger in the segmentally stenosed shunt vessels than in the uniformly patent shunt vessels ($p < 0·001$). The ratio in the two shunt vessels only partially imaged by cross sectional echocardiography indicated that they were segmentally stenosed.**

***Conclusion*—The combination of cross sectional and Doppler echocardiography may be useful for determining either the patency or the morphology of an aortopulmonary shunt.**

Aorta to pulmonary artery shunts are widely used as a palliative treatment of congenital heart disease in patients with decreased pulmonary blood flow. Auscultation of the shunt murmur and analysis of the haematocrit and arterial blood gases have all been used as indirect indicators of shunt patency. Cross sectional and Doppler echocardiography have also been used to evaluate heart function and anatomy at the bedside.

We have already reported a non-invasive Doppler echocardiographic method of evaluating the shunt flow dynamics of the ductus arteriosus.[1] To our knowledge, however, previous studies have not directly analysed shunt vessel morphology or the shunt flow.[2 3] We have investigated the usefulness of cross sectional and Doppler echocardiography for the bedside evaluation of the patency and morphology of the aortopulmonary shunt.

Patients and methods

PATIENTS

We studied 12 patients with various cyanotic congenital heart diseases who had shunt operations performed in our hospital. Two of them had had repeat operations because their first shunt operations were clinically not effective. Diagnoses were confirmed by diagnostic cardiac catheterisation. The shunt operations were left Blalock-Taussig shunt operation (nine patients), right Blalock-Taussig shunt (three patients), modified Waterston shunt (one patient), and a central shunt (ascending aorta to main pulmonary artery anastomosis) (one patient). Only one (patient 6) of the nine patients with a left Blalock-Taussig shunt had a modified Blalock-Taussig shunt operation with a polytetrafluoroethylene graft (table 1).

DOPPLER ECHOCARDIOGRAPHIC TECHNIQUE

We used a commercially available cross sectional echocardiograph. Hewlett Packard Model 77020AC, that incorporated a pulsed Doppler flow meter in an ultrasonic wide angle phased array system. Ultrasonic frequencies of 5 MHz (shallow focus) and 3·5 MHz were used. We also used continuous Doppler methods when aliasing occurred with the pulsed Doppler method.

The examination was performed with the patient in a supine position. If necessary, a small pillow was placed under the shoulder in order to extend the neck.

Cross sectional and Doppler echocardiographic examinations were performed through suprasternal or high parasternal windows for patients with left Blalock-Taussig shunt. The transducer was directed to image the aortic arch and to search for the aortic orifice of the shunt vessel, the left subclavian artery, or the left brachiocephalic artery. Once the orifice was located the distal portion of the shunt vessel was imaged by rotating the beam clockwise through 20° to 30° (fig 1). The suprasternal approach was also used in the patient with a right Blalock-Taussig shunt. The transducer was directed at the aortic arch in the long axis plane in order to detect the orifice of the shunt vessel. Shunt vessels could then be imaged by

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Table 1 Data on the study patients

Patient	*Sex*	*Age*	*Diagnosis*	*Shunt*
1	F	5 mnth	TOF	l-BT
2	F	5 mnth	TOF, Down's syndrome	l-BT, r-BT
3	M	5 yr	TOF	l-BT
4	M	5 yr 6 mnth	TA (la), PDA	l-BT
5	M	5 yr 10 mnth	TA (la)	l-BT, central
6	F	9 yr 4 mnth	TA (lb)	l-BT
7	F	2 mnth	TGA, ASD, VSD, Co/Ao	r-BT
8	F	6 yr 5 mnth	TGA, VSD, PS	l-BT
9	F	2 mnth	Dextro, UVH, Malposition GA, PA, PDA, PLSVC, r-Ao A	l-BT
10	M	3 mnth	CAVC, TGA, SA, PDA, asplenia	r-BT
11	M	3 mnth	Dextro, SA, UVH, PA, PDA, r-Ao A	l-BT
12	M	8 yr 5 mnth	UVH, Malposition GA, PA, PDA, PFO, r-Ao A	Modified Waterston

ASD, atrial septal defect; CAVC, common atrioventricular canal; Co/Ao, coarctation of the aorta; dextro, dextrocardia; l-BT, left Blalock-Taussig shunt; GA, malposition of the great arteries; PA, pulmonary atresia; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PLSVC, patent left superior vena cava; PS, pulmonary stenosis; r-Ao A, right aortic arch; r-BT, right Blalock-Taussig shunt; SA, single atrium; TA, tricuspid atresia; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart; VSD, ventricular septal defect.

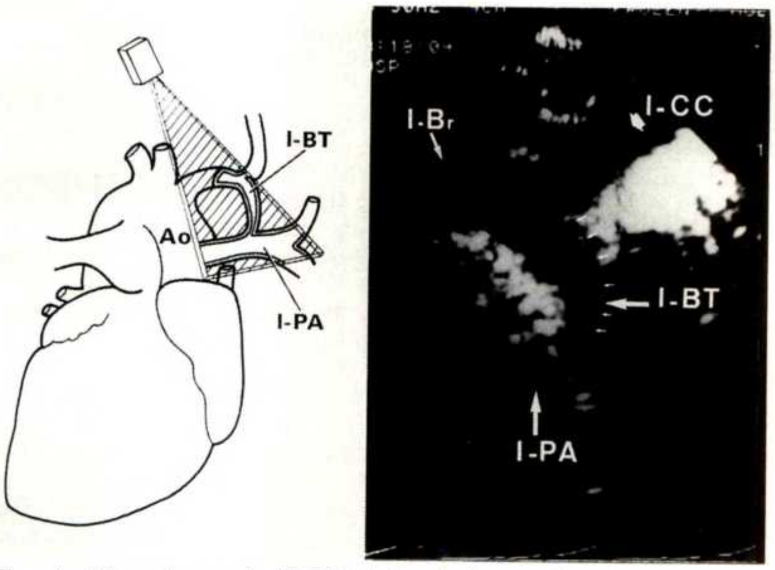

Figure 1 Echocardiogram of a left Blalock-Taussig shunt vessel (patient 11). Ao, aorta; l-Br, left brachiocephalic artery; l-BT, left Blalock-Taussig shunt vessel; l-CC, left common carotid artery; l-PA, left pulmonary artery.

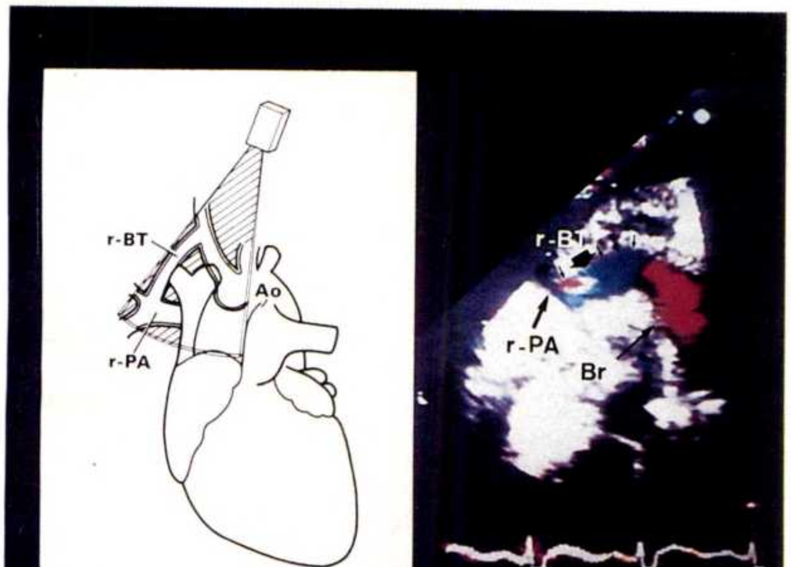

Figure 2 Echocardiogram of a right Blalock-Taussig shunt vessel from the suprasternal window (patient 7). Colour Doppler showed flow away from the transducer (blue signal) in the shunt vessel. A red signal was seen in the distal portion of the shunt vessel because of the high shunt flow velocity. Ao, aorta; r-BT, right Blalock-Taussig shunt vessel; Br, brachiocephalic artery; r-PA, right pulmonary artery.

tilting the transducer by 10°–20° laterally to the right (fig 2). The parasternal approach was used in the patient with a central shunt or modified Waterston shunt. The transducer was placed at the mid left sternal border and directed transversely at the ascending aorta. The shunt vessel was imaged beyond the transversely sectioned ascending aorta in the patient with a modified Waterston shunt (fig 3).

Colour Doppler echocardiography was also used to aid the detection of the shunt vessels in 10 patients examined towards the end of this study. Flow directed toward the transducer was conventionally coded in red and flow away from the transducer was coded in blue.

When the shunt vessel was detected, the internal diameter was measured (from inner edge to inner edge) with the callipers incorporated in the equipment and the Doppler sample volume was then positioned within the shunt vessel. The shunt flow was recorded with the electrocardiogram and a video recorder. The peak flow velocity (cm/s) was measured at proximal and distal sites in the shunt vessels. In a few patients where the flow velocity at the distal site exceeded the highest range that could be recorded by the pulsed Doppler method we measured the peak flow velocity by the continuous Doppler method. In addition, the peak flow velocity at the proximal and intermediate sites was measured at the same time to confirm that the value measured by the continuous Doppler method was being recorded at the distal site.

The peak flow velocity measured in the distal portion of the shunt vessel was compared with that measured in the proximal portion. The ratio between the peak flow velocity at the distal portion and at the proximal portion was then calculated.

ANGIOGRAPHY

Cardiac catheterisation and angiography were performed in 10 patients a few days after the Doppler and echocardiographic examination. The shunt vessels were selectively imaged by biplanar cineangiography.

STATISTICAL ANALYSIS

Grouped data were compared by the unpaired Student's t test. A p value of $\leq 0{\cdot}05$ was regarded as significant.

Results

Twelve of 14 shunt vessels were imaged along their entire length (85·7% success rate). The distal portions of the shunt vessels were not detected in two patients (cases 5 and 8, both with a left Blalock-Taussig shunt). In the 10 patients who also had angiography the echocardiographic and angiographic appearances of the shunt vessels were identical (fig 4). Figure 4 shows the cross sectional echocardiogram of a left Blalock-Taussig shunt (patient 11). Shunt flow was detected in both the proximal and distal portions (fig 4). Right Blalock-Taussig shunts, the modified Waterston shunt, and the central shunt were also clearly imaged.

Stenosis of the shunt vessel was tentatively

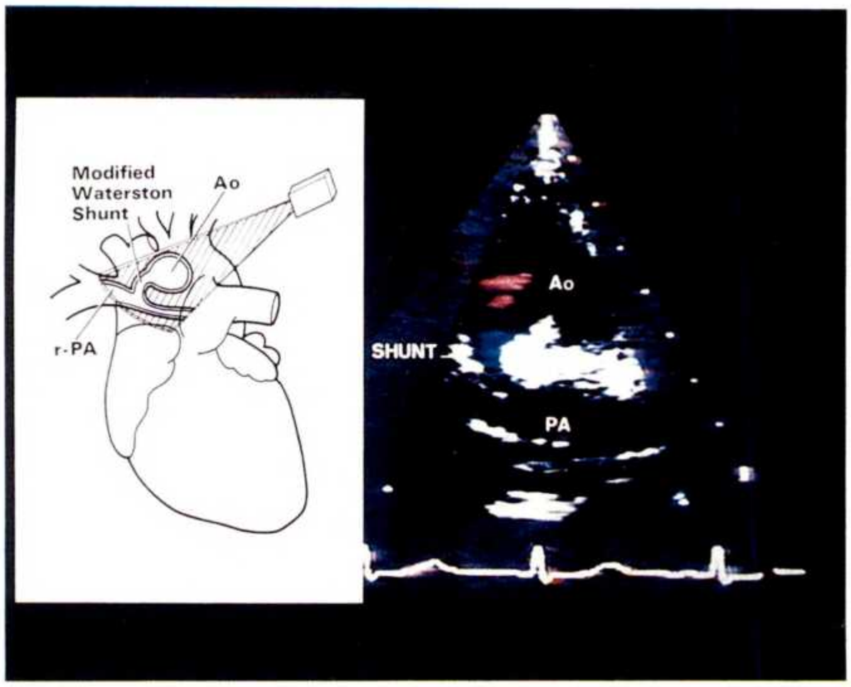

Figure 3 Echocardiogram of a modified Waterston shunt (patient 12) from the parasternal window. The transducer was transversely directed towards the ascending aorta. The shunt vessel was detected beyond the ascending aorta. Ao, ascending aorta; r-PA, right pulmonary artery; Shunt, modified Waterston shunt.

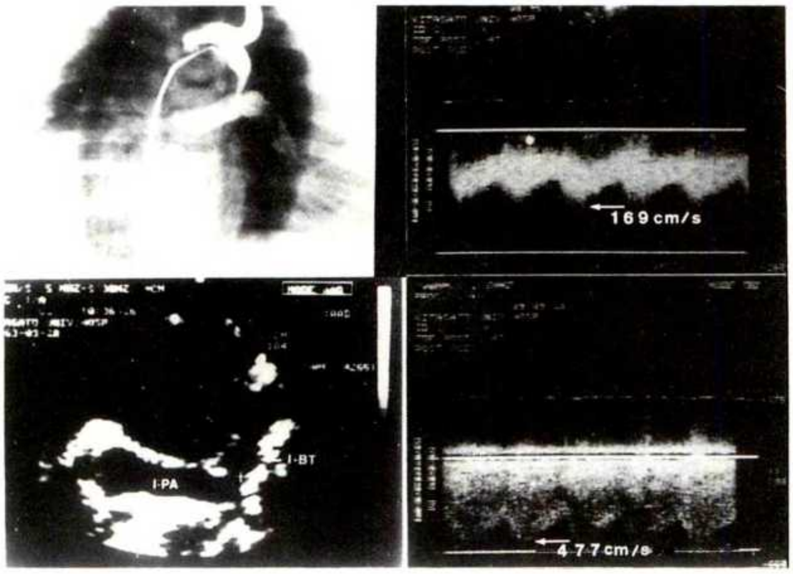

Figure 4 Angiogram and echocardiogram of a left Blalock-Taussig shunt vessel. The entire shunt vessel was imaged by the cross sectional echocardiography. The shape shown by echocardiography was almost identical to that shown by angiography. Shunt flow was detected by a pulsed Doppler method not only in the proximal portion (right upper) but also at the distal portion (right lower). Because peak flow velocity at the distal site was so high the continuous Doppler method was used to detect the shunt flow. l-BT, left Blalock-Taussig shunt vessel; l-PA, left pulmonary artery.

diagnosed when the diameter of the shunt vessel was less than 2·5 mm. Six of 12 shunt vessels had diameters of $>2·5$ mm along their entire length by cross sectional echocardiography (uniformly patent shunt vessels). The diameter of four other shunt vessels was $<2·5$ mm at their distal sites (segmentally stenosed shunt vessels), and the diameters of the remaining two shunts were $<2·5$ mm along their entire length (uniformly stenosed shunt vessels).

The ratio of the peak flow velocity in the distal portion to that in the proximal portion was 0·89–1·46 in uniformly patent shunt vessels (n = 6), 1·87–2·82 in segmentally stenosed shunt vessels (n = 4), and 1·38 and 2·41 in the two patients with uniformly stenosed shunt vessels (table 2). Segmentally stenosed shunt vessels had significantly larger ratios than uniformly patent shunt vessels ($p < 0·001$).

In the two patients in whom the distal portions of the shunt vessels were not imaged by cross sectional echocardiography (patients 5 and 8, both with left Blalock-Taussig shunt) the peak flow velocity was also measured by the continuous Doppler method at the distal sites. The ratio of the peak flow velocity measured by the continuous Doppler method in the distal portion to that in the proximal portion indicated segmentally stenosed shunt vessels. Angiograms in these two patients showed stenosis at the distal sites.

Discussion

IDENTIFICATION OF THE SHUNT VESSELS

The shunt vessels were clearly imaged by our cross sectional echocardiographic method, although in two patients the distal portion was not imaged. The echocardiographic and angiographic findings showed similar shunt vessel morphology.

PATENCY OF THE SHUNT VESSELS AND FLOW VELOCITIES

Continuous left-to-right shunt flow was detected within all the shunt vessels. Shunt flow velocity was measured in the proximal and distal portions of the 12 shunt vessels. Peak flow velocity was very high in the distal portion of segmentally stenosed shunt vessels. The ratio of peak flow velocity in the distal portion to the peak flow velocity in the proximal portion in this group was larger than that of uniformly patent shunt vessels. The ratios were 1·38 and 2·41 in two patients with uniformly stenosed shunt vessels. The diameter of the left Blalock-Taussig shunt in the patient with a ratio of 1·38 was 2·0 mm at the proximal portion and 1·9 mm at the distal portion. In the patient with a ratio of 2·41 the diameters were 2·1 mm and 1·3 mm respectively. The tapering shape of this shunt vessel is thought to have caused the high ratio. In the two patients with uniformly stenotic shunts, oxygenation had not improved and second palliative operations were performed. These findings indicate that measurement of the ratio of the peak flow velocity at the distal portion to the peak flow velocity at the proximal portion will improve the accuracy of the evaluation of shunt vessel morphology.

Moreover, in the patients in whom the distal site could not be detected by cross sectional echocardiography, we were able to assess the segmental stenosis at the distal site of the shunt vessels by taking the peak flow velocity at the distal site to be the same value as that detected by the continuous Doppler method. These cases illustrate the usefulness of combining the pulsed Doppler and continuous Doppler methods to assess shunt vessel morphology.

Table 2 Ratio of the peak flow velocity in the distal portion to that in the proximal portion

Patient no (type)	*D/P*
Uniformly patent	
4 (l-BT)	0·98
5 (central)	1·44
6 (l-BT)	1·19
7 (r-BT)	1·46
10 (r-BT)	1·20
12 (central)	0·89
Segmentally stenosed	
2 (r-BT)	1·95
3 (l-BT)	2·27
9 (l-BT)	1·87
11 (l-BT)	2·82
Uniformly stenosed	
1 (l-BT)	2·41
2 (l-BT)	1·39

D/P, ratio of proximal peak flow to distal peak flow. See footnote to table 1 for other abbreviations.

Marx *et al* reported that continuous Doppler echocardiography could detect shunt flow and could be used to estimate the drop in pressure across aorta to pulmonary artery shunts.[3] They used the suprasternal notch or the supraclavicular window for Blalock-Taussig shunts and the left parasternal window for Waterston shunts. They did not, however, mention the morphology or size of the shunt vessels. Our study shows that the beam direction is vital when the peak flow velocity is being measured especially in patients with a segmentally stenotic shunt vessel.

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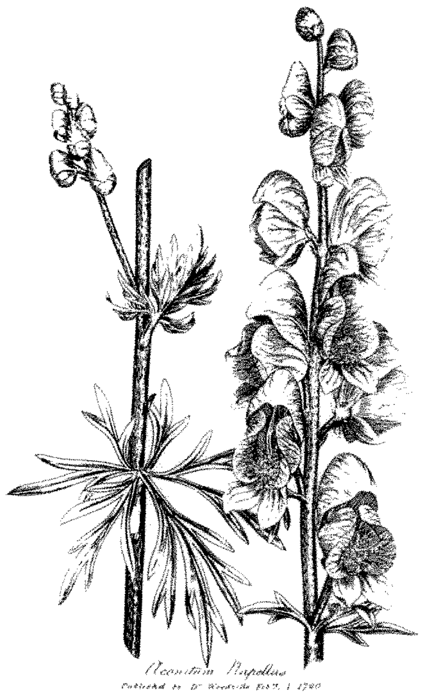
1 Hiraishi S, Horiguchi Y, Misawa H, *et al.* Noninvasive Doppler echocardiographic evaluation of shunt flow dynamics of the ductus arteriosus. *Circulation* 1987;75:1146–53.
2 Allen HD, Sahn DJ, Lange L, *et al.* Noninvasive assessment of surgical systemic to pulmonary artery shunts by range-gated pulsed Doppler echocardiography. *J Pediatr* 1979;**94**:395–402.
3 Marx GR, Allen HD, Goldberg SJ. Doppler echocardiographic estimation of systolic pulmonary artery pressure in patients with aortic-pulmonary shunts. *J Am Coll Cardiol* 1986;7:880–5.

PLANTS IN CARDIOLOGY

Aconitine and arrhythmias

Various species of aconite, *Aconitum* (Ranunculaceae), such as wolfsbane and monkshood, have been known as deadly poisons since the time of ancient Greece (Medea used aconite to kill Theseus). Soon after the leaf or root is eaten a characteristic tingling spreads over the body, the voluntary muscles twitch, the pulse becomes irregular and weak, and death inexorably follows in a few hours. Animal studies in the nineteenth century showed that the alkaloid aconitine produced vagal slowing followed by an irregular rhythm; and in 1897 S A Matthews at Ann Arbor, using the myocardiograph, became the first to show that it causes atrial and ventricular fibrillation (*Journal of Experimental Medicine* 1897;**2**:593–606). In 1909 in the first paper of the new journal *Heart* A R Cushny showed that it caused pulsus alternans in dogs.

Despite its reputation aconite became a popular medicine and was used to treat neuralgia, fever, pericarditis, and nervous palpitation. In 1869 Sydney Ringer wrote "Perhaps no drug is more valuable than aconite." But in 1880 a patient became very ill when the source of his tincture was unknowingly changed to a different aconite root, and his physician Dr Meyer died after taking a dose to justify the safety of his prescription.



The Linnean Society.

Aconitum napellus L. Woodville W. *Medical Botany*. London: Woodville, 1790; volume 1: page 16.

It was the work of David Scherf that established the special place of aconitine in experimental arrhythmias. In 1947 he showed that when aconitine was injected into the sinus node of dogs it was better than faradisation in producing episodes of atrial fibrillation or flutter that were long enough to assess the effect of antiarrhythmic drugs. Myron Prinzmetal used topical aconitine for his high-speed cinematograph studies of atrial arrhythmias in 1952.

The family Ranunculaceae has 58 genera and 1750 species mostly in temperate regions. Many of them are poisonous because they contain benzyl isoquinoline and other alkaloids, and some species of *Ranunculus* (buttercup) cause photodermatitis. The genera *Adonis* (pheasant's eye) and *Helleborus* (Christmas rose) contain cardiac glycosides but they are not used medicinally and neither are any other species.

It could still be rewarding to study the cellular mechanism of aconitine induced arrhythmias.

A HOLLMAN

Br Heart J 1992;67:316–20

Morphological study of defects of the atrial septum within the oval fossa: implications for transcatheter closure of left-to-right shunt

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Abstract

Objective—To determine the anatomical variability of the oval fossa in cases of atrial septal defect and to find out which factors might make such defects suitable or unsuitable for closure by umbrella or clamshell devices.

Design—100 specimens with defects of the atrial septum within the oval fossa were studied, especially the position of the defects within the fossa; the area of the defect in relation to the total area of the oval fossa; the shape of the rims and flap valve of the oval fossa; and the anatomical variability in the eustachian and thebesian valves.

Results—The oval fossa was displaced to the mouth of the inferior caval vein in four cases; displaced to the mouth of superior caval vein in two cases; placed on the middle of the interatrial wall in 43; or placed slightly towards the inferior caval vein in 51. Because of their shape 29 of the hearts were considered to be unsuitable for transcatheter closure of the defect. This was because the defect was too large (16 hearts); the oval fossa was displaced to the mouth of the inferior caval vein (four hearts) or to the superior caval vein (two hearts); lacked its anterior rim (two hearts); lacked the posteroinferior rim (one heart); because a thick eustachian valve was displaced posteriorly forming a false posteroinferior rim (one heart); or because the strand of insertion of the floor of the oval fossa was too distant from the left atrial aspect (three hearts).

Conclusion—68 hearts appeared to be ideal candidates for transcatheter closure; 3 would probably have been suitable; but 29 were unsuitable. These morphological variations might explain why the procedure has been unsuccessful in so many cases. Patients should be screened before any attempt is made at transcatheter closure.

In the past three decades there have been many advances in the use of interventional techniques in the treatment of congenital malformations of the heart including those of the atrial septum.[1] Morphological studies show[2 3] that not all communications that permit an interatrial shunt, and not even all those within the oval fossa, will be suitable for closure in this fashion. The refinements made in interventional cardiology, therefore, make it necessary to know the nature and extent of the morphological patterns of the oval fossa, and particularly of its deficiencies, which could interfere in closure by umbrella or clamshell devices. With this need in mind, we have investigated the variable anatomical patterns of deficiencies of the floor of the oval fossa, its muscular rims, and its relation to the other structures separating the cavities of the right and left atria. In this way, we hoped to identify difficulties that might occur during the introduction of catheters and the placement of the occluding device. We also hoped to identify the proportion of cases that might be unsuitable for non-surgical closure.

Methods

There are 352 specimens with deficiencies of the oval fossa in the cardiopathological collection of the Department of Paediatrics of the National Heart and Lung Institute of the University of London. From these we selected the first 100 specimens that were suitable for detailed analysis.

We selected hearts of any size or age in which the oval fossa had not been torn by Rashkind's procedure or repaired surgically. We also excluded any specimens in which associated cardiac malformations might have distorted the atrial septum, such as juxtaposition of the appendages, extreme hypoplasia of the left or right heart, criss-cross hearts, and so on. Specimens with other forms of interatrial communication (sinus venosus, ostium primum, and "coronary sinus" defects[2 3]) were also excluded.

We measured the longest and shortest diameters of each oval fossa. The radius of the circle was obtained by the formula $(X + Y)/4$. Afterwards we estimated the size of the fossa by drawing the defect within the idealised circle of the fossa on graph paper. In this way, we calculated the proportion of the floor of the fossa that was deficient.

In all specimens we concentrated our descriptions on the right atrial aspect of the oval fossa. We looked at the position of the defect within the fossa, the position of the fossa on the walls between the atria, the extension of the defect towards the mouths of either the inferior or superior caval veins, the texture and the pattern of the flap valve of the fossa (the septum primum), the shape of the muscular rim, and the size and texture of the eustachian and thebesian valves.

In each heart we then examined the left atrial aspect of the septum, noting any unusual muscle bands or undue proximity of the right pulmonary veins that might have made placement of a device inappropriate.

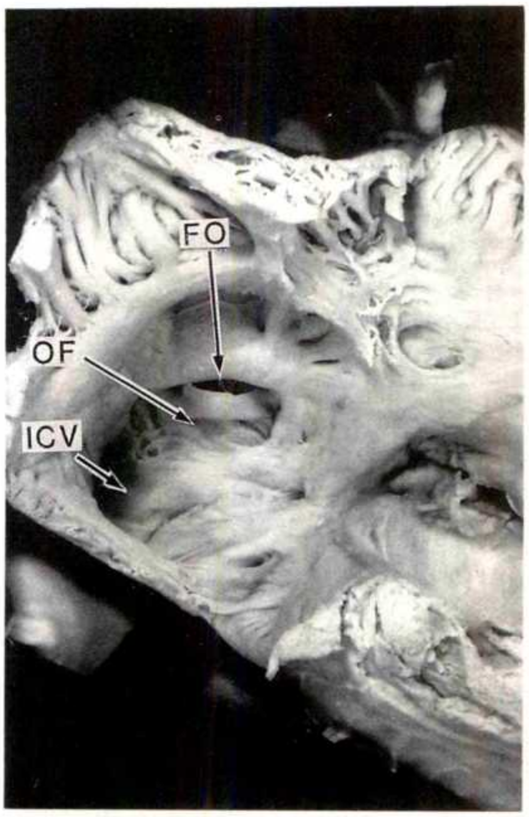

Figure 1 Specimen showing the oval fossa (OF) normally situated and slightly tilted towards the inferior caval vein (ICV) and a widely patent foramen ovale (FO).

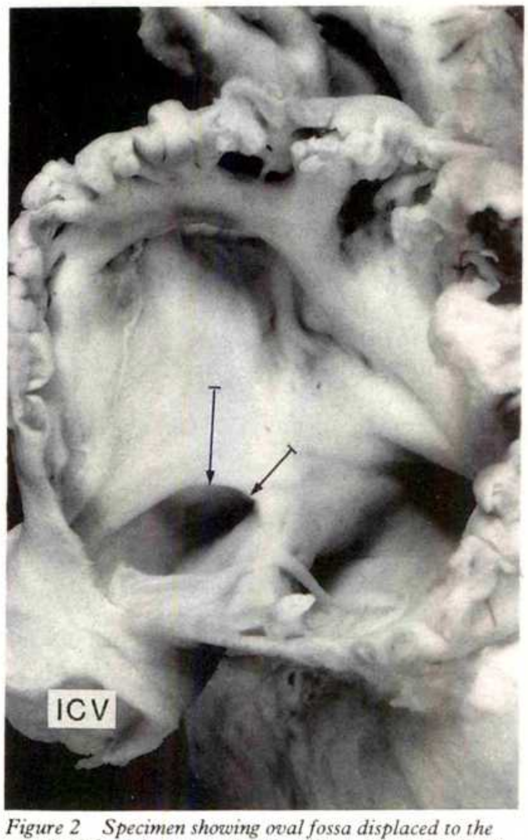

Figure 2 Specimen showing oval fossa displaced to the mouth of the inferior caval vein (ICV). Note the size of the anterosuperior and anteroinferior rims (arrows).

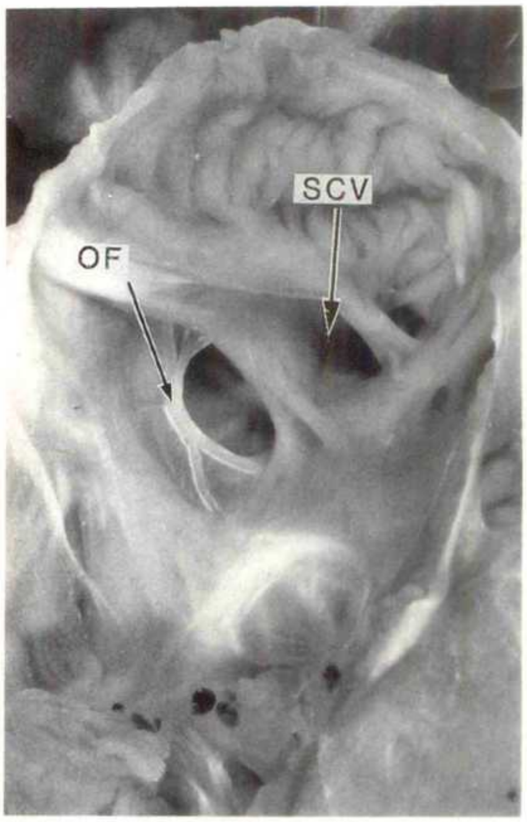

Figure 3 Specimen showing the oval fossa (OF) displaced to the mouth of the superior caval vein (SCV).

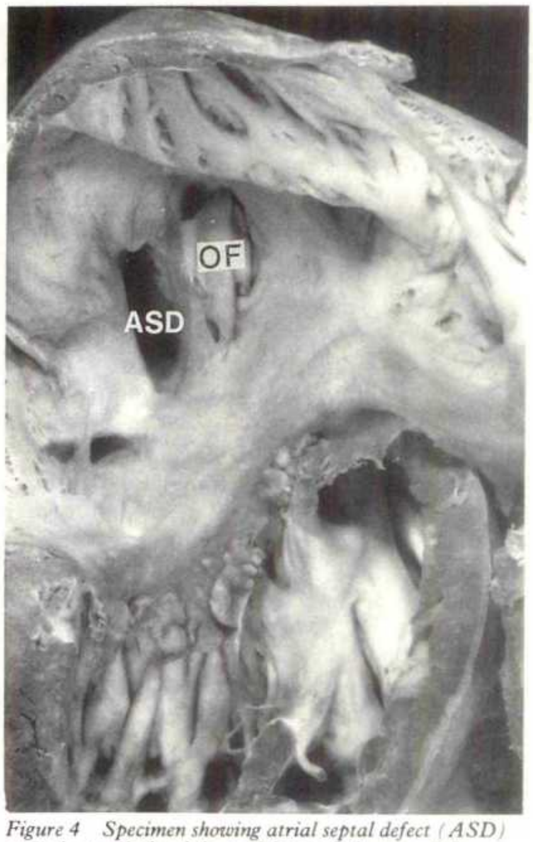

Figure 4 Specimen showing atrial septal defect (ASD) opened posteriorly of the oval fossa (OF) toward the posterior wall of the atria.

Results

The youngest specimen examined came from a neonate of six hours, and the oldest was from a patient aged 35 years. There were 31 specimens from patients whose age was not known, but as far as could be judged from size most of them came from young children. Of the 100 hearts chosen for analysis, 17 had a patent oval foramen but no deficiency of the flap valve (fig 1). In 12 of the hearts the defect occupied 50% or more of the total area of the fossa. In four there was complete absence of the flap valve while, in the remaining 67 hearts, the size of the defect was less than 50% of the area of the oval fossa. The oval fossa was slightly tilted towards the mouth of the inferior caval vein in 51 hearts (fig 1). It occupied the middle of the interatrial wall in 43 but was obviously displaced to the mouth of the inferior caval vein in four (fig 2). In the other two it was displaced towards the mouth of the superior caval vein (fig 3).

In 99 of the hearts, the deficiency of the floor was directed towards the anterior rim of the fossa or else to the anteroinferior rim. In only one of the hearts was the defect found to open posteriorly towards the back of the atria (fig 4).

In 83 hearts the fossa was indeed oval, with the longest diameter taking various directions. In only 17 was the fossa round. Its floor was very thick and muscular in 48, moderately thick in 27, thin in 18, showing a pattern of filigreed remnants in three, and virtually absent in the other four (table 1). Six hearts had fenestrated floors. In five of these the flap valve was very thin whereas in the remaining one it was thick.

The shape of the rims of the fossa also varied considerably. The rim was well delineated all around the fossa in 67 hearts. In contrast, it was well delineated anterosuperiorly but exhibited a flat posteroinferior border in 21. In another eight of the hearts all the border was flat without any obvious rim. There was no anterior rim in two of the hearts (fig 5) and no posterior rim in one. In the final heart, the eustachian valve was so thick and posteriorly displaced that it formed a false posteroinferior rim (fig 6).

The eustachian and thebesian valves, when identified, could be categorised according to their texture, thickness, and size: namely, muscular (irrespective of size); large and thin; small and thin; or rudimentary (table 2). In half of the cases, however, we could not find the valves, either because they had been completely resorbed, which seemed to be the situation in most, or because they had been removed during pathological examination.

Viewed from the left atrial aspect, the fossa was adjacent to the right superior pulmonary veins in three hearts (fig 7). The strand of insertion of the flap valve was far from the limits of the fossa in another three hearts (fig 8).

Table 1 Patterns of the floor of the oval fossa

Pattern	*No*
Very thick and muscular	48
Moderately thick	27
Thin	18
Filigreed remnant	3
Absent	4

Our observations indicated that undue difficulties might have been encountered in closing the defects by means of a device in 29 hearts. In 16 hearts this was because the defect was too

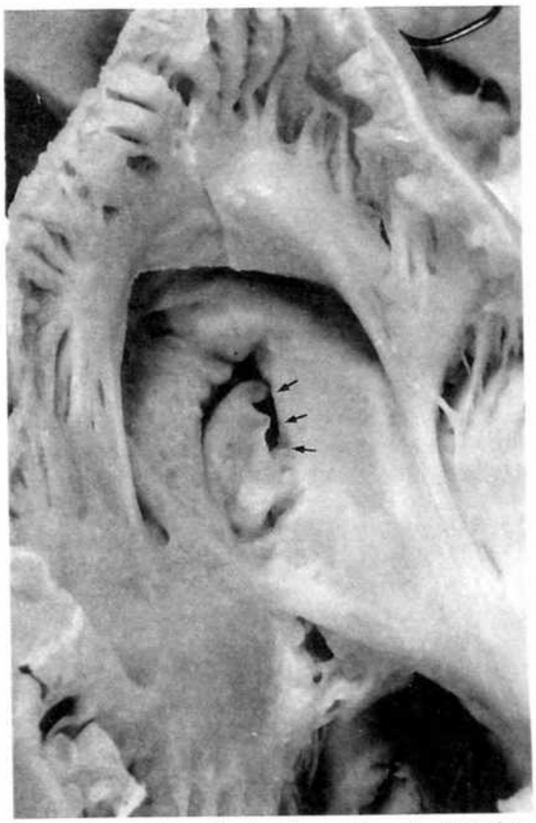

Figure 5 Specimen showing the oval fossa in which there is no anterior rim to anchor a device (arrows).

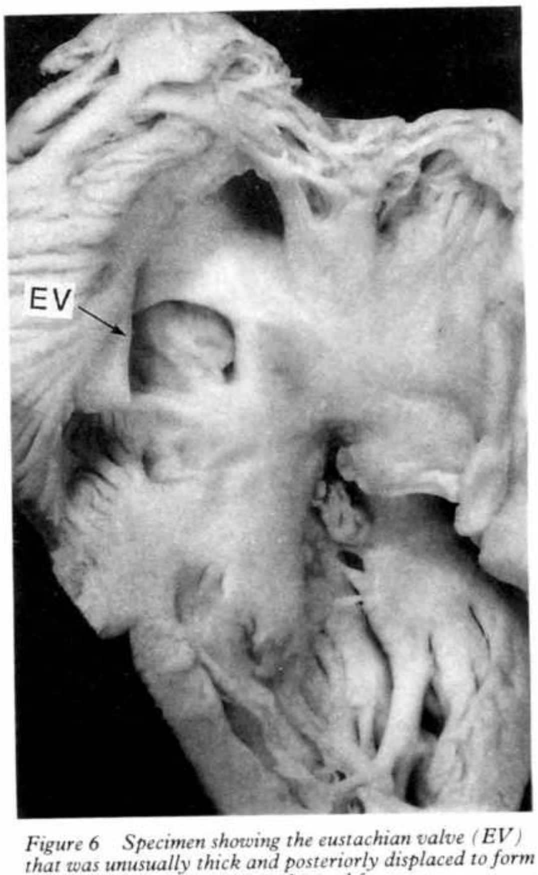

Figure 6 Specimen showing the eustachian valve (EV) that was unusually thick and posteriorly displaced to form a false posteroinferior rim to the oval fossa.

large, either as a consequence of complete lack of development of the flap valve or because the defect was larger than half the area of the oval fossa. In four hearts it was because of displacement of the fossa towards the mouth of the inferior caval vein (in three of these the oval fossa, on its left atrial aspect, was also adjacent to the right superior pulmonary veins), and because it extended towards the mouth of the superior caval vein in two. There was no anterior rim and no obvious facility to anchor the device in two hearts and no posteroinferior rim in one heart where the defect was situated adjacent to the posterior wall of the atria. The eustachian valve formed a false posteroinferior rim to the defect in one heart. In the three remaining hearts, the flap valve in the left atrium was inserted so far from the rim of the fossa that it could have allowed residual flow after attempted closure.

Table 2 Patterns of eustachian and thebesian valves

Pattern	*Eustachian*	*Thebesian*
Muscular (irrespective of size)	6	2
Large and thin	19	15
Small and thin	10	10
Rudimentary	15	26
Not seen*	50	47

*Completely resorbed or removed during pathological examination.

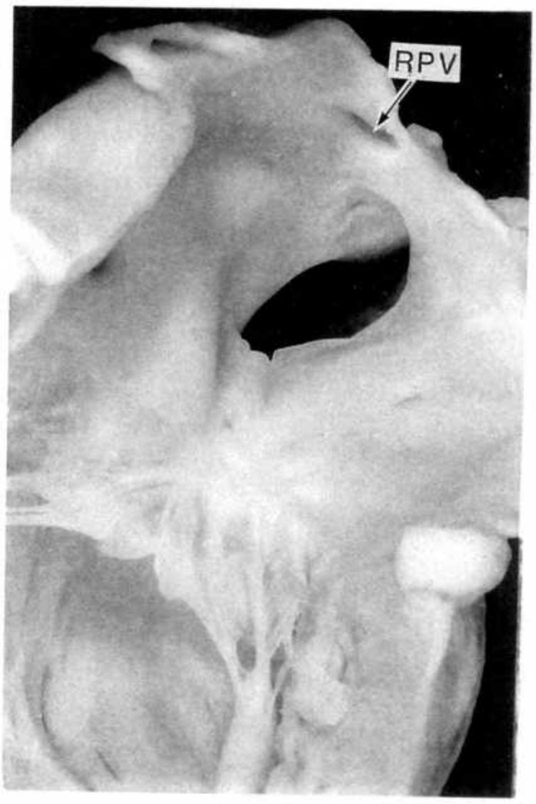

Figure 7 Specimen showing the oval fossa viewed from the left atrial aspect adjacent to the right pulmonary veins (RPV).

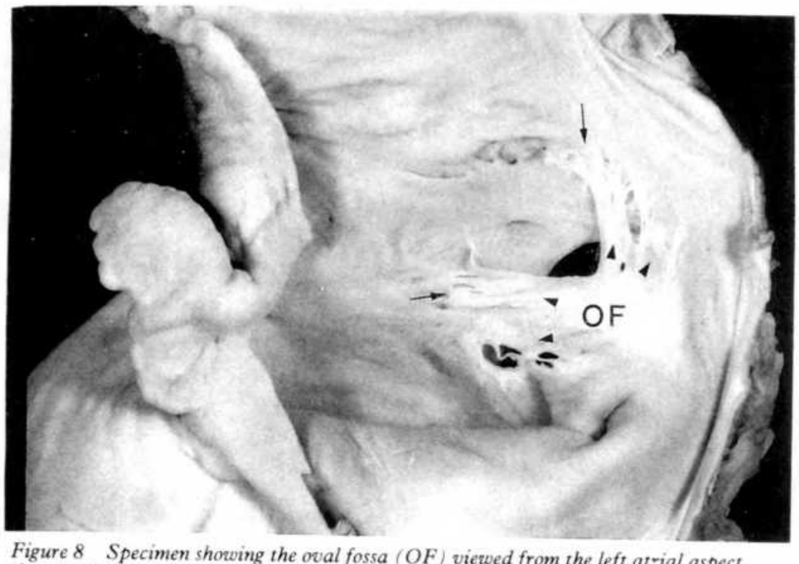

Figure 8 Specimen showing the oval fossa (OF) viewed from the left atrial aspect showing the insertion of the flap valve (arrows) far from its usual attachment (arrow heads).

Other problems that could have caused technical difficulties in manoeuvring the sheath inside the right atrium were found in three hearts. There was hypertrophy of the terminal crest in two and presence of a large and muscular eustachian valve in the other. In one further heart a slit was discovered within the sinus septum which if undetected would have remained as an additional communication between the atria.

Discussion

Interventional cardiology has made it possible to close atrial septal defects in selected patients with devices inserted through catheters.[1] A better understanding of the types of defects in the oval fossa that would be suitable for closure by this method, and those in which such attempted closure may be contra-indicated, depends on a full understanding of the anatomy of the oval fossa and the surrounding tissue. While others have examined the anatomy of the rim of the oval fossa and also its proximity to vital structures within the atria,[4,5] the anatomical variability of these structures has rarely been considered. We carefully examined 100 postmortem specimens and noted the size and variability of deficiencies of the oval fossa in each.

From the right atrial aspect the atrial wall extends from the orifices of the superior and inferior caval veins to the attachment of the septal leaflet of the tricuspid valve. Within this extensive area only the oval fossa and its immediate rims separate the cavities of the two atrial chambers. Any hole outside this area is not, by definition, an atrial septal defect but rather an interatrial communication.[2] By virtue of the more complex arrangement of such communications, it is only deficiencies within the oval fossa that, in the first instance, are likely to be suitable for closure by devices introduced on catheters. We have concentrated on defects in the oval fossa.

The results of our study suggest that some anatomical arrangements are not amenable to transcatheter repair. The location of the oval fossa was grossly abnormal in four specimens—that is, situated directly in front of the mouth of the inferior caval vein. Not only would this position make it difficult to distinguish the defect from an interatrial communication of the inferior sinus venosus type, but such holes would also be difficult to close without impeding flow from the inferior caval vein. In these cases, the posteroinferior rim may be too small to anchor the device satisfactorily without leaving a residual shunt. This was also true of two specimens in which the oval fossa was situated adjacent to the entrance of the superior caval vein.

Some studies have highlighted inadequacy of a muscular rim around the defect as a cause of embolisation of the device.[1, 5] We found five examples of this arrangement out of the 100 hearts we examined. Two lacked the anterior rim and one lacked the posterior rim, while the other two, where the defect was displaced to the mouth of the superior caval vein, lacked the superior rim.

Clinical experience has shown that the diameter of the device used for attempted closure must be 10 to 15 mm greater than the area of the septal deficiency,[6] or at least 1·6 times the diameter of the defect as determined by sizing with balloons at catheterisation.[5] The defect was equal to or bigger than half the area of the oval fossa in 16 of these hearts. This would rule out attempted closure.

There may also be problems if the flap valve on the left atrial aspect is inserted far from the rim of the fossa. Depending upon its extent such malinsertion could also cause some malalignment between the oval fossa and its flap valve, thereby allowing a residual flow after placement of the occluding device.

Apart from the major considerations discussed above, other minor impediments can prevent successful closure by a transcatheter technique. Thus the size, thickness, and proximity of the septal insertion of the eustachian valve may cause it to be "caught" by a device. In one heart we also found a hypertrophied terminal crest that formed a muscular bar across the right atrial cavity near its roof. Such an arrangement could have trapped the catheter sheath. More commonly (18 hearts), however, we noted that the very thin floors of the oval fossa could have been torn by traction on the sheath.

In this study we included 17 specimens where the oval foramen was widely patent because the primary septum was not fused, but the flap valve itself was not deficient. We included these because later the indication for transcatheter closure may be broadened. It could be used in some particular groups of patients who late in life have unsaturation at the atrial level because of increased pressure in the right side of the heart, patients who have percutaneous dilatation of the mitral valve, a procedure that leaves a shunt[7, 8] at the atrial level, and the large number of young patients with a patent oval foramen in whom stroke may be caused by paradoxical embolism.[9]

Only 68 of the 100 hearts we examined appeared to be ideal for transcatheter closure. Three hearts would probably have been suitable. In 29, however, we found anatomical impediments that would have countervailed against successful closure. It is always unwise to predict the impossibility of future closure on the basis of study of necropsied hearts, as shown by the apparent success of balloon dilatation of native coarctation despite histological studies pointing to its inadvisability. Our study does indicate, none the less, that, at least initially, great care should be exercised and only ideal cases should be referred for attempted closure of defects of the atrial septum.

1 Rocchini AP. Transcatheter closure of atrial septal defects: past, present and future. *Circulation* 1990;82:1044–5.

2 Beerman LB, Zuberbuhler FR. Atrial septal defect. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology*. Edinburgh: Churchill Livingstone, 1989:541–62.

3 Ettedgui JA, Siewers RD, Anderson RH, Park SC, Pahl E, Zuberbuhler JR. Diagnostic echocardiographic features of the sinus venosus defect. *Br Heart J* 1990;64:329–31.

4 Lock JE, Rome JJ, Davis R, Van Praagh S, Perry SB, Van Praagh R, *et al.* Transcatheter closure of atrial septal defect: experimental studies. *Circulation* 1989;79:1091–9.

5 Rome JJ, Keane JF, Stanton BP, Spevak PJ, Lock JE. Double-Umbrella closure of atrial septal defects: initial clinical applications. *Circulation* 1990;82:751–8.

6 King TD, Thompson SL, Steiner C, Mills NL. Secundum atrial septal defect: nonoperative closure during cardiac catheterization. *JAMA* 1976;235:2507–9.

7 L'Epine Y, Drobinski G, Sotirov Y, Moussallem N, Voudris V, Komajda M, *et al.* Right heart failure due to an interatrial shunt after mitral balloon dilatation. *Eur Heart J* 1989;10:285–7.

8 Goldberg N, Roman CF, Cha SD, Weiner R, Maranhao V, Elderdge J, *et al.* Right to left interatrial shunting following balloon mitral valvuloplasty. *Cathet Cardiovasc Diagn* 1989;16:133–5.

9 Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, *et al.* Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148–52.

Br Heart J 1992;**67**:321–2

CASE REPORTS

Severe haemolysis after transcatheter duct occlusion: a non-surgical remedy

Alison M Hayes, A N Redington, M L Rigby

Abstract

Severe mechanical haemolysis occurred in a seven month old infant after the insertion of a 17 mm Rashkind double umbrella device. The placement of a second device 23 days after the initial procedure abolished haemolysis.

Transcatheter occlusion with the Rashkind double umbrella device is now widely accepted as treatment for small and moderate sized arterial ducts. The reported complications include embolisation of the device, pseudocoarctation, left pulmonary artery stenosis, residual shunts, and mechanical haemolysis.[1-3] We describe a case of severe mechanical haemolysis resulting from incomplete closure after placement of a 17 mm Rashkind occluder. Complete closure was achieved and the haemolysis ceased when a second 17 mm device was inserted.

Case report

A seven month old infant was referred for cardiac assessment because of a cardiac murmur. The clinical findings were consistent with a persistent arterial duct. The chest radiograph showed cardiomegaly and pulmonary plethora. Cross sectional echocardiography confirmed the presence of a moderate sized persistent arterial duct with left ventricular volume overload. Cardiac catheterisation was performed when the child was 13 months old and weighed 10 kg. The preliminary aortogram showed a large arterial duct which was 6 mm in diameter. A 17 mm Rashkind double umbrella device was placed in a good position without difficulty. However, a further aortogram indicated some residual left to right flow through the duct, above the device (fig 1A). Doppler echocardiography 24 hours later confirmed a small residual shunt.

Two weeks later the child re-presented with pallor and a history of haematuria, jaundice, and vomiting. The haemoglobin was 54 g/l. Red cell fragments and polychromasia were noted on the blood film and the reticulocyte count was 23%. After a blood transfusion (haemoglobin 117 g/l) the haemolysis continued and there was further haemoglobinuria. Forty eight hours later the haemoglobin concentration had fallen to 95 g/l. Cross sectional echocardiography indicated appropriate placement of the original device, though the distal prongs could be seen projecting into the aorta. In view of continued severe haemolysis cardiac catheterisation was undertaken 23 days after the original procedure. The initial aortogram showed a large residual shunt through the duct. A second 17 mm Rashkind double umbrella was placed without complication (fig 1B). Initial Doppler studies after the procedure showed a trivial residual shunt which on review at one month had disappeared. There was no further haemolysis. The haemoglobin concentration one month after the second procedure was 131 g/l and the reticulocyte count was 0·8%.

Discussion

There have been two previous reports of severe mechanical haemolysis after percutaneous transcatheter duct occlusion.[2 3] In one the device was removed surgically and the duct was ligated.[2] It was thought that the haemolysis in this patient, who also had a small "residual leak", may have been related to the poor position of the device, with the proximal arms impinging on the left pulmonary artery. This was not true of our patient. It is much more likely that red cell destruction was caused by a high velocity jet of blood passing over or through the device within the duct. Furthermore, because of the late presentation we were concerned that surgical removal might prove difficult and possibly require cardiopulmonary bypass. We therefore elected to place a second device. The placement of a second device for a residual left to right shunt has been described previously.[1 4] In the Toronto series 5·7% of patients required a second 12 mm double umbrella because of important residual flow after the initial procedure. Five of the six had successful reocclusion.

To our knowledge the successful use of a second umbrella to treat severe mechanical haemolysis has been reported only once before by Rohmer and colleagues when they described the initial experience of percutaneous duct occlusion in the Netherlands.[3] The second umbrella also promptly stopped the haemolysis.

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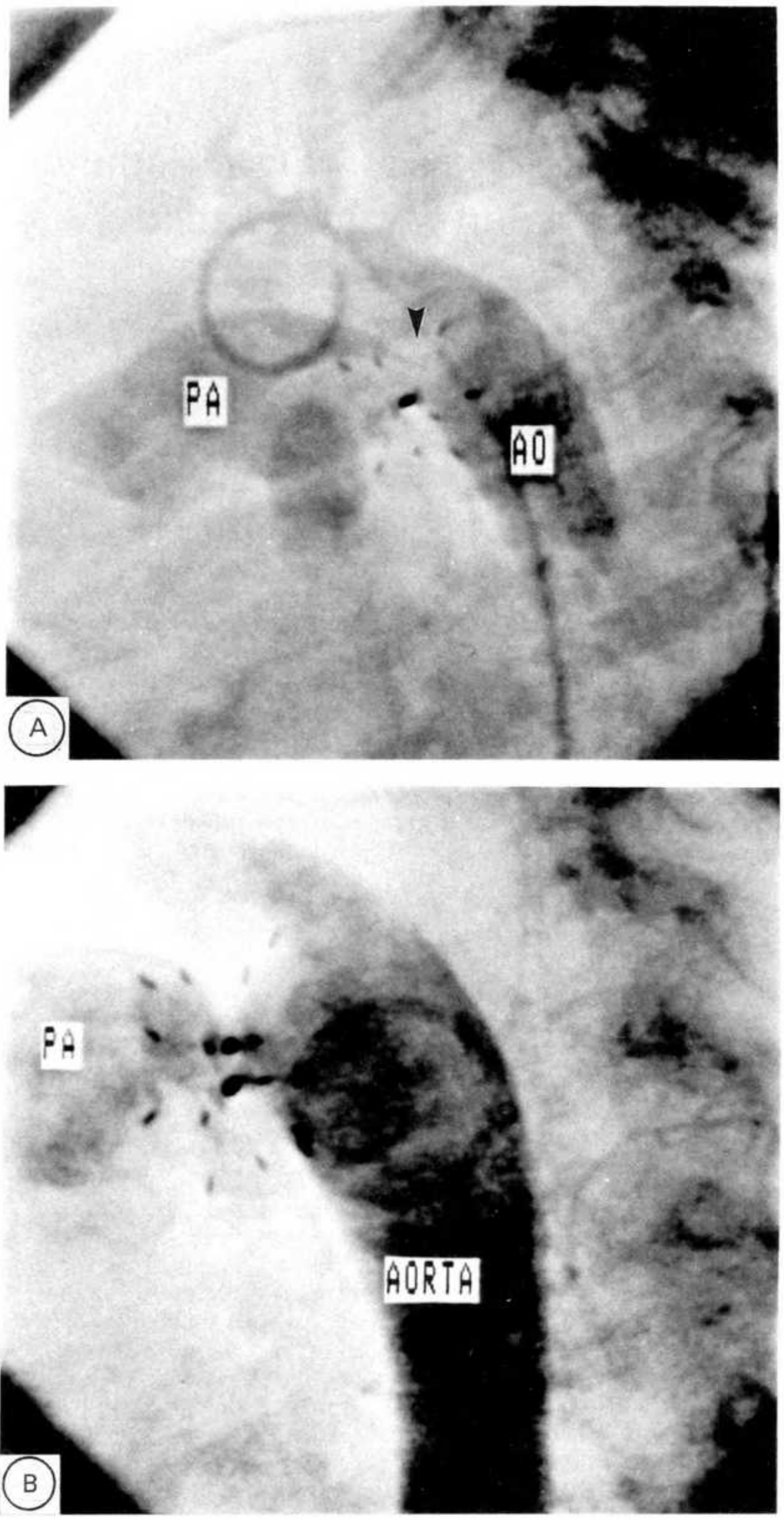
Figure (A) Aortogram showing satisfactory positioning of the first 17 mm device. There was a significant residual left to right shunt above the device (arrow).
(B) A further aortogram showing two 17 mm Rashkind double umbrellas positioned in the duct. At this stage, immediately after release of the second device, there was a small residual leak through the fabric of the umbrellas.



1 Rashkind WJ, Mullins CE, Hellenbrand WE, Tait MA. Nonsurgical closure of patent ductus arteriosus: clinical application of the Rashkind PDA Occluder System. *Circulation* 1987;**75**:583–92.

2 Ladusans EJ, Murdoch I, Franciosi J. Severe haemolysis after percutaneous closure of a ductus arteriosus (arterial duct). *Br Heart J* 1989;**61**:548–50.

3 Rohmer J, Hess J, Talsma MD. Closure of the persistent ductus arteriosus (Botalli) using a catheter procedure; the initial 50 patients treated in The Netherlands. *Ned Tijdschr Geneeskd* 1990;**134**:2347–51.

4 Hosking MC, Benson LN, Musewe N, Freedom RM. Reocclusion for persistent shunting after catheter placement of the Rashkind patent ductus arteriosus occluder. *Can J Cardiol* 1989;**5**:340–2.

Br Heart J 1992;**67**:323–4

Spontaneously acquired fistula from the right coronary artery to the right ventricular cavity

S G Ray, M D Cowan, J A Kennedy

Abstract

A 47 year old man developed a fistula from the right ventricular branch of the right coronary artery to the right ventricular cavity in association with distal occlusion of the main trunk of the right coronary artery. There was no clinical or electrocardiographic evidence of acute myocardial infarction.

The development of coronary artery fistulas after myocardial infarction has been reported but is very rare.[1 2] We report a case of an acquired right coronary artery fistula to the right ventricle in association with arterial occlusion but without electrocardiographic evidence or a clinical diagnosis of myocardial infarction.

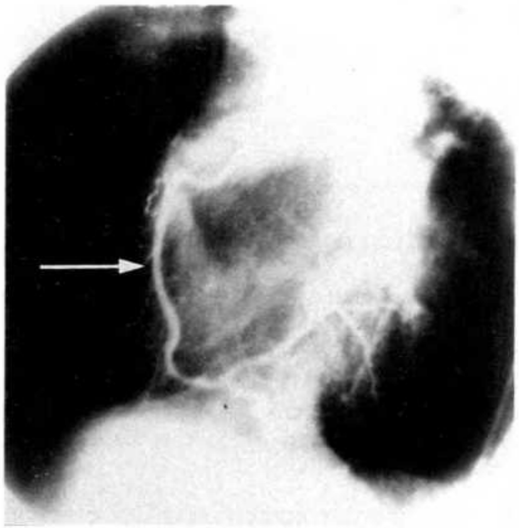


Figure 1 60° Left anterior oblique view of the right coronary artery in 1982.

Case report

A 42 year old white man presented in November 1982 with an anterior myocardial infarction. Left ventricular angiography in the convalescent period showed a small antero-apical aneurysm but good global ventricular function. At coronary angiography there was a 50% diameter stenosis in the left anterior descending artery and minor atheromatous change in the right coronary artery (fig 1). Medical treatment was continued and he made an uneventful recovery and subsequently did not attend for follow up examination.

In May 1987 he was readmitted with prolonged ischaemic chest pain brought on by exercise. There was no evidence of myocardial infarction and his resting electrocardiogram was unchanged from that in 1982. Exercise testing showed considerable inferior ischaemia, and he underwent repeat cardiac catheterisation in April 1988. On this occasion there was considerable hypokinesia of the inferior and posterior portions of the left ventricle. There was a 70% diameter stenosis of the left anterior descending artery and a 50% diameter stenosis of the obtuse marginal branch of the circumflex artery. The previously dominant right coronary artery was occluded (fig 2) and filled to the crux from the left. There was a tight stenosis of the right

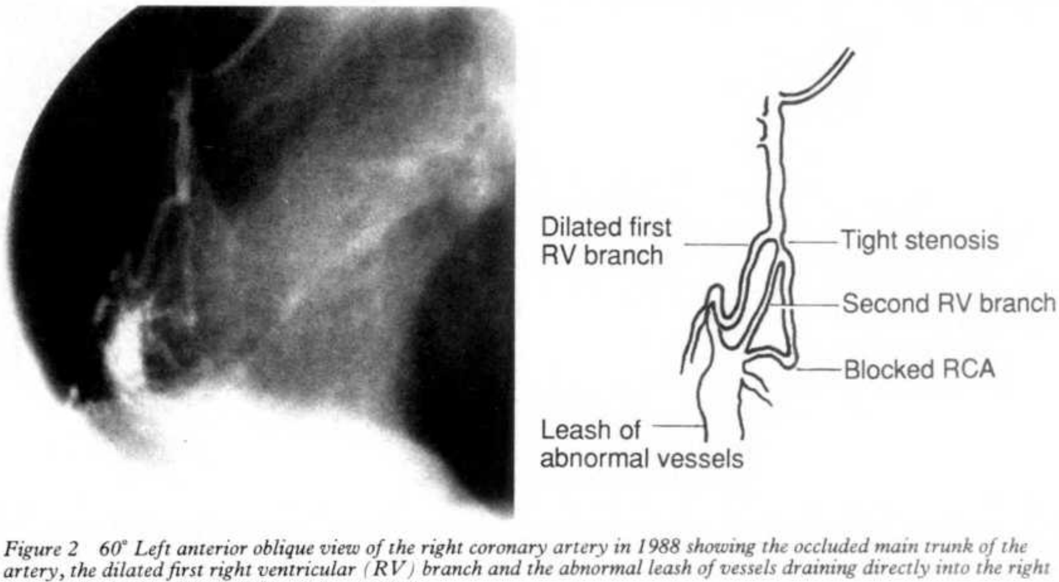


Figure 2 60° Left anterior oblique view of the right coronary artery in 1988 showing the occluded main trunk of the artery, the dilated first right ventricular (RV) branch and the abnormal leash of vessels draining directly into the right ventricular cavity. RCA, right coronary artery.

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coronary artery just distal to its first right ventricular branch, which was considerably dilated and (together with several smaller vessels) was feeding an abnormal leash of vessels draining directly into the right ventricular cavity.

He underwent coronary artery bypass grafting. At operation there was no suggestion of a tumour and the inferior surface of the heart was free of important scarring, which accorded with the lack of electrocardiographic or clinical evidence of a second infarct. The dilated first right ventricular branch of the right coronary artery was identified and tied off distally. No other abnormal vessels could be visualised.

Discussion

We are aware of one report of an angiography documented acquired coronary artery fistula after myocardial infarction in which a fistula developed from the diagonal branch of the left anterior descending artery and communicated with the left ventricular cavity.[1] At rest our patient had considerable wall motion abnormality in the territory of the right coronary artery but no history or electrocardiographic changes suggestive of infarction. Chronic ischaemia produced by progressive occlusion of the right coronary artery could have caused the wall motion abnormality while at the same time acting as the stimulus for the development of collateral vessels from the first right ventricular branch. Aberrant development of collateral vessels then led to fistula formation. Myocardial ischaemia in patients with congenital and acquired coronary artery fistulas has been attributed to coronary steal.[1,3] The development of the fistula in our patient could have coincided with the worsening of ischaemia and his readmission in 1987.

We thank Mr M P G Jamieson for permission to report the surgical findings.

1 Yu R, Sharma B, Franciosa JA. Acquired coronary artery fistula to the left ventricle after acute myocardial infarction. *Am J Cardiol* 1986;**58**:557–8.

2 Ryan C, Gertz EW. Fistula from coronary arteries to left ventricle after myocardial infarction. *Br Heart J* 1977; **39**:1147–9.

3 Wilde P, Watt I. Congenital coronary artery fistulae: six new cases with a collective review. *Clin Radiol* 1980;**31**:301–11.

ABSTRACTS IN CARDIOLOGY

Familial dilated cardiomyopathy—not so rare

We all know that inheritance plays a part in dilated cardiomyopathy: the question is how big a part. This study from the Mayo Clinic suggests that one in five patients with dilated cardiomyopathy will have one or more relatives who fulfil the diagnostic criteria for dilated cardiomyopathy. The prevalence of familial disease is likely to be greater than the 20% reported, as an additional 28 patients (9%) from 22 families were considered to be of indeterminate status. There are no clinical features that distinguish familial from nonfamilial disease.

WILLIAM J McKENNA

The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy

Virginia V Michels, Patricia P Moll, Fletcher A Miller, A Jamil Tajik, Julia S Chu, David J Driscoll, John C Burnett, Richard J Rodeheffer, James H Chesebro, Henry D Tazelaar

Background—Dilated cardiomyopathy is characterised by an increase in ventricular size and impairment of ventricular function. Most cases are believed to be sporadic, and familial dilated cardiomyopathy is usually considered to be a rare and distinct disorder. We studied the proportion of cases of idiopathic dilated cardiomyopathy that were familial in a large sequential series of patients whose first-degree relatives were investigated regardless of whether these relatives had cardiac symptoms.

Methods—We studied the relatives of 59 index patients with idiopathic dilated cardiomyopathy by obtaining a family history and performing a physical examination, electrocardiography, and two-dimensional, M-mode, and Doppler echocardiography. A total of 315 relatives were examined.

Results—Eighteen relatives from 12 families were shown to have dilated cardiomyopathy. Thus, 12 of the 59 index patients (20·3 percent) had familial disease. There was no difference in age, sex, severity of disease, exposure to selected environmental factors, or electrocardiographic or echocardiographic features between the index patients with familial disease and those with nonfamilial disease. A noteworthy finding was that 22 of 240 healthy relatives (9·2 percent) with normal ejection fractions had increased left ventricular diameters during systole or diastole (or both), as compared with 2 of 112 healthy control subjects (1·8 percent) who were studied separately.

Conclusions—Dilated cardiomyopathy was found to be familial in at least one in five of the patients in this study, a considerably higher percentage than in previous reports. This finding has important implications for family screening and provides direction for further investigation into the causes and natural history of dilated cardiomyopathy. (*N Engl J Med* 1992;**326**:77–82.)

Br Heart J 1992;67:325–33

Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest (new abridged version)

The "Utstein Style"

Prepared by a task force of representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, and Australian Resuscitation Council

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I Introduction

Representatives from the European Resuscitation Council and the American Heart Association met on two occasions in 1990 to establish uniform terms and definitions for out-of-hospital resuscitation. The first meeting took place at the historic Utstein Abbey near Stavanger in Norway; the second (which also included representatives of the Heart and Stroke Foundation of Canada and the Australian Resuscitation Council) was in Surrey, England.

The European Resuscitation Council was formed in August 1989 as a multinational and multidisciplinary group that includes representatives from the European Society of Cardiology, the European Academy of Anaesthesiology, the European Society for Intensive Care Medicine, and related national societies. The other three major participating organisations have a long tradition of involvement in matters relating to resuscitation.

Resuscitation has become an important multidisciplinary branch of medicine, calling for a range of skills and attracting a plethora of specialities and organisations. Each of these organisations claims a legitimate interest in the science and practice of resuscitation. This complex background has hindered the development of consistent terminology. Moreover, no uniform pattern exists for reporting results. Different systems cannot readily be compared or contrasted because data are rarely compatible.

The new recommendations are intended to promote more effective exchange of information and to improve international audit. The "Utstein style" is the designation favoured by the participants. It comprises a glossary of agreed terms and a template for reporting resuscitation attempts relating to out-of-hospital cardiac arrest. The template covers a list of events that should be included in reports, definitions of time points and time intervals related to cardiac resuscitation, and recommendations for the description of emergency medical resuscitation systems. This article presents a modified and abridged version of the agreement relating to the Utstein style. The full report with appropriate references has been (or will be) published in five national and international journals that have special relevance to resuscitation.[1-5] The abridged version will also be published elsewhere.[6] The Utstein document, or sections of it, will be subject to further revision if necessary.

II Glossary of terms

The nomenclature of cardiac arrest presents a classic problem in semantics—the same term has different meanings for different people. The Utstein definitions and recommendations attempt to solve this problem by presenting consensus definitions. The 11 items included in the international glossary were chosen because they gave rise to misunderstandings during the conference. Common definitions were agreed as a preliminary step to achieving compatibility in reporting results.

Cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, by unresponsiveness, and by apnoea (or agonal, gasping respirations). For the purposes of the Utstein style no comment on time or "suddenness" is recommended.

Cardiopulmonary resuscitation (CPR) is a broad term meaning the *act of attempting* to achieve restoration of spontaneous circulation. CPR is an action: it can be successful or unsuccessful and *basic* or *advanced* (see below).

Basic CPR is the act of attempting to restore an effective circulation using *external* compressions of the chest wall plus inflation of the lungs with *expired* air. Rescuers can provide the ventilation through airway adjuncts and face shields appropriate for use by the lay public. This definition excludes the bag valve mask, invasive techniques of airway maintenance such as intubation of the airway, and any airway devices that pass the pharynx.

Basic cardiac life support This term, especially in the United States, has an expanded meaning beyond the term basic CPR. It includes an entire educational programme that provides information about access to the emergency system and recognition of a cardiac arrest, as well as basic CPR.

Advanced CPR, advanced cardiac life support, ACLS These terms refer to the act of attempting to restore spontaneous circulation by using basic CPR *plus* advanced airway management and ventilation techniques, defibrillation, and intravenous or endotracheal medications.

Bystander CPR, lay responder CPR, citizen CPR Of these synonymous terms the consensus conference preferred bystander CPR. This is basic CPR performed by someone who is *not* part of an organised response system. In general this will be the person who witnessed the arrest. In certain situations, therefore, physicians, nurses, and paramedical staff may perform bystander or (more appropriately) professional first-responder CPR.

Emergency personnel are individuals who respond to a medical emergency in an official capacity as part of an organised response team. By this definition physicians, nurses, or paramedical staff who witness a cardiac arrest in a public setting and initiate CPR but who have *not* responded to the event as part of an organised team are *not* emergency personnel.

Cardiac aetiology (presumed) Treatment of cardiac arrest presumed to be due to heart disease represents the principal activity of most pre-hospital emergency systems. It is impractical for researchers to determine accurately the specific cause of cardiac arrest for all attempted resuscitations. For the purposes of the Utstein reporting template researchers should classify cardiac arrests as having a presumed cardiac aetiology if this is likely on the basis of all available information. This is often a diagnosis by exclusion.

Non-cardiac aetiology While this represents a disparate collection of causes, they are often obvious and readily determined. Specific subcategories include sudden infant death syndrome, drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid haemorrhage, and trauma.

Automated external defibrillators (AEDs) This generic term refers to defibrillators that perform rhythm analysis of the patients' surface electrocardiogram to detect ventricular fibrillation or rapid ventricular tachycardia. The information provided to the operator is usually presented as "shock" or "no shock indicated", leaving the operator to trigger the electrical discharge.

Times v intervals Imprecision and inconsistency in the use of *times* and *intervals* has produced much confusion and misunderstanding in publications about cardiac arrest. The word *interval*, rather than *time*, refers to the period between two events. The definition of the interval should be clear from the expression used, and not be dependent on emergency jargon. The format for expression of intervals should be *event-(to)-event interval*, with an explicit statement of the two relevant events.

III Template for reporting data from cardiac arrest

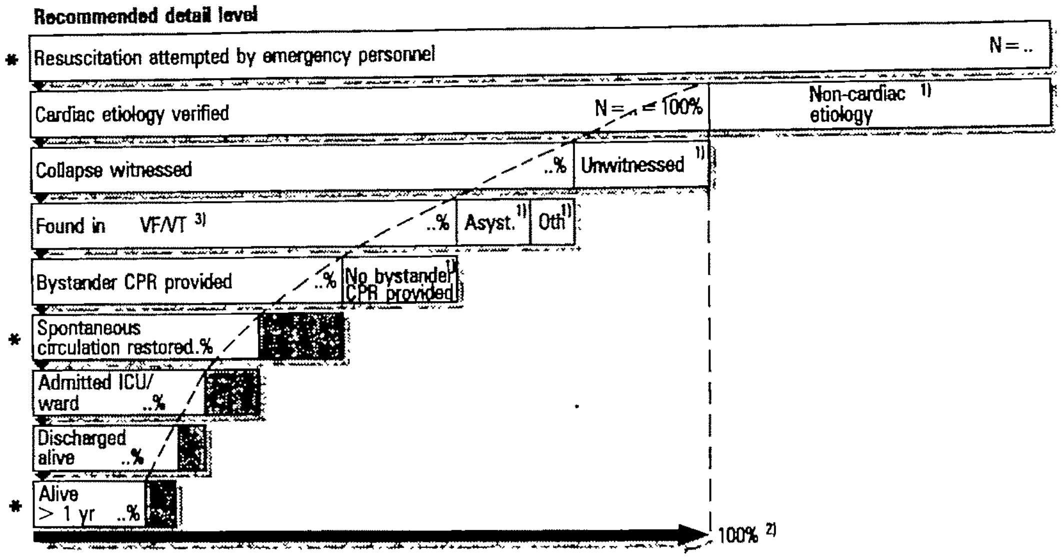
CORE DATA AND OPTIMAL DATA

The Utstein pattern for reporting results of resuscitation attempts should enable workers in all countries to have data in a format that permits national and international comparisons and audit. Until now, disparity in definitions and lack of uniformity in clinical variables have led to difficulties and misunderstandings that have hindered progress. But resources, research intentions, and opportunities for publication vary widely; it follows that some reports will be much more detailed than others. The concept of *core* and *optimal* data was therefore introduced. The intention is to encourage all workers in the field to obtain what we regard as minimal information to provide core data for the evaluation of pre-hospital resuscitation schemes. Other workers engaged in key projects of major epidemiological importance are likely to seek more detailed information and that too should be in a format that permits comparisons. These more comprehensive requirements have been collated into a set of optimal data. Some studies, inevitably, will fall between these extremes; all data can be evaluated provided they are based on agreed definitions and fall within the patterns that are proposed. Similarly, even reports with less than core data can provide a useful contribution if agreed definitions are used. This report will emphasise particularly the core data that are requested for all publications on pre hospital resuscitation because only specialised workers will be likely to collect more. All with a major interest in the epidemiology or practice of resuscitation should consult the full publications[1–5] before designing protocols.

THE TEMPLATE APPROACH

The consensus conference participants recommended the template approach for reporting data relating to the pre-hospital management of victims of cardiac arrest. Figure 1 shows the outcome information that researchers should include in their reports. The top bar represents the total of all victims on whom resuscitation attempts were made by emergency personnel. But the true denominator for evaluating the success rate of resuscitation is the total of the patients with a verified cardiac aetiology for their arrests; those with non-cardiac causes form a heterogenous group who would introduce too many confounding variables that would differ from one scheme to another. Many consider that the best test of the efficiency of a system is the result obtained in the treatment of witnessed cardiac arrest from ventricular fibrillation. Figure 1 also shows how the denominator falls from level to level down to the minority who survive one year after resuscitation.

Figure 1 . Utstein II recommendations on data to be reported on cardiac arrest resuscitation.



* Minimum data level

1) Subgroups with an additional survival potential which may be analyzed using an identical pattern, i.e. broken into the lower steps in the template

2) For purposes of uniform reporting the recommended "100%", or denominator group, is resuscitations attempted on cardiac arrests of cardiac etiology

3) VT should be reported as a separate group

Figure 2 shows the Utstein style template for full data collection on cardiac arrest. The template calls for a number to be inserted for each level. These numbers will permit researchers to calculate multiple rates, because a figure at each level serves two functions: the numerator for the level above, and the denominator for the level below. The template begins with the population served by the emergency system and displays how various exit points occur before and after arrival at the *cardiac aetiology* box that will provide the denominator for assessing outcome success in fig 1. Figure 2 comprises 22 boxes in all, each identified by a unique number, but the rectangular boxes in the central column provide the key information. Most of the other data can be derived from them. Use of this scheme by an emergency system will permit immediate comparisons with all other systems that have used the template and have made known their results. The paragraph numbers below correspond to the identification of the boxes in fig 2. Most relate to the important data in the central column.

(1) Population Served

This starting point permits calculation of the population-based incidence of cardiac arrest as well as population-based survival rates. The total population of a community is a useful figure *only* when the entire population resides within the specific service area served by the emergency system. The methods section of any report on cardiac arrest outcomes should include some description of the community including the percentage of the population over age 65. The area served by the system (in square kilometres) should also be part of the core data.

(2) Confirmed cardiac arrests considered for resuscitation

These include *all* unresponsive, breathless, and pulseless patients for whom the emergency personnel are called. The emergency personnel must confirm the cardiac arrests. A record should also be made of the number of patients in whom resuscitation was attempted by lay rescuers (either ventilation attempts, chest compressions, or both) but whom the emergency personnel observed to have a pulse upon arrival. This additional subgroup permits an assessment of possible lay person "rescues" but may include false positive cardiac arrests and respiratory arrests. Reports should tabulate this group separately and not in the total of confirmed cardiac arrests.

(4) Resuscitations attempted by emergency personnel

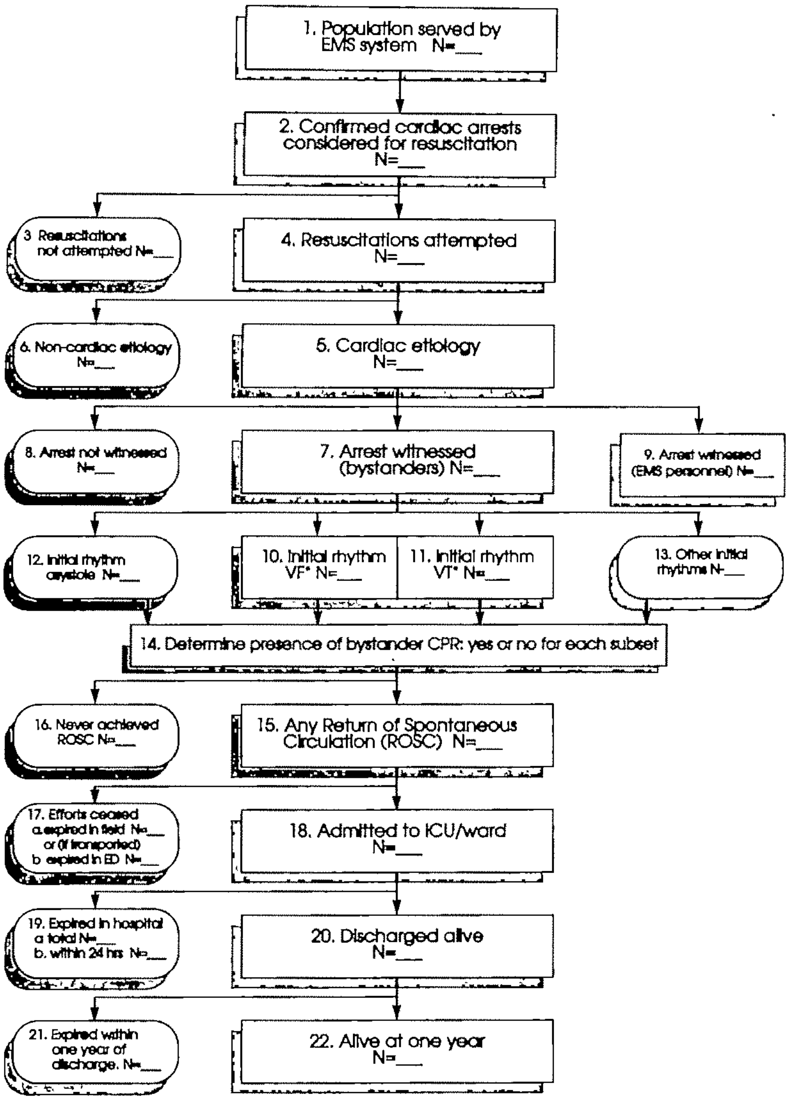
This group includes all people for whom any emergency system personnel made attempts at resuscitation (other than basic assessment). A *resuscitation attempt* means at least some effort at basic CPR. This definition implies that this section of the template will contain some victims on whom a resuscitation effort was abandoned when it was recognised to be inappropriate.

(5) Cardiac aetiology (see glossary)

Emergency personnel should determine the presence and duration of any antecedent signs and symptoms of ischaemia. Primary electrical events that are cardiac in origin—for example so-called sudden cardiac death—may be unheralded and these may present a problem of classification. The conference accepted that this category was partly one of exclusion of other known causes and recognised the inevitability that classification may not be precise.

(7) Witnessed arrests

The recommended focus of the Utstein template is arrests that are witnessed. These are arrests in which a bystander or emergency personnel or both saw or heard the patient collapse. The Utstein template displays unwitnessed arrests, like arrests of non-cardiac


1. Population served by EMS system N=___
2. Confirmed cardiac arrests considered for resuscitation N=___
3 Resuscitations not attempted N=___
4. Resuscitations attempted N=___
6. Non-cardiac etiology N=___
5. Cardiac etiology N=___
8. Arrest not witnessed N=___
7. Arrest witnessed (bystanders) N=___
9. Arrest witnessed (EMS personnel) N=___
12. Initial rhythm asystole N=___
10. Initial rhythm VF* N=___
11. Initial rhythm VT* N=___
13. Other initial rhythms N=___
14. Determine presence of bystander CPR: yes or no for each subset
16. Never achieved ROSC N=___
15. Any Return of Spontaneous Circulation (ROSC) N=___
17. Efforts ceased a. expired in field N=___ or (if transported) b expired in ED N=___
18. Admitted to ICU/ward N=___
19. Expired in hospital a total N=___ b. within 24 hrs N=___
20. Discharged alive N=___
21. Expired within one year of discharge. N=___
22. Alive at one year N=___

*VF and VT should be reported separately through template

Figure 2 Recommended "Utstein style" template for reporting data on cardiac arrest.

aetiology, as "exit" categories. Most reports of pre-hospital cardiac arrest observe that approximately 10% occur after the arrival of emergency personnel. The Utstein style recommends that these *arrests after arrival* patients be separated (box 9) from the unwitnessed arrests and from the arrests witnessed by bystanders.

(10) Ventricular fibrillation

Subdivisions of ventricular fibrillation such as fine, moderate, or coarse are of limited clinical usefulness. A specific distinction, however, between fine ventricular fibrillation and asystole, while clinically and physiologically indeterminate, should be made for the purposes of uniform reporting. The Utstein style recommends a specific though arbitrary distinction between asystole and fine ventricular fibrillation: a deflection on the surface electrocardiogram of less than 1 mm amplitude (calibrated at 10 mm/mV) will be considered to be asystole; 1 mm or greater will be considered to be ventricular fibrillation. Automated external defibrillators already use this criterion.

(11) Ventricular tachycardia

Because it has a different range of outcomes the consensus conference recommended that pulseless ventricular tachycardia should not be grouped with ventricular fibrillation but should have a separate template pathway. These patients are, however, such a small proportion of the cases of out-of-hospital cardiac arrest that they are often combined with the much larger number of patients with ventricular fibrillation.

(13) Other rhythms

This category includes the rhythms in which some electrical activity is observed in a patient who will not survive cardiac arrest. The activity usually appears as wide ventricular escape complexes that probably represent the last electrical activity of a dying heart. There is little to be gained by detailed refinement of this category. "Electromechanical dissociation" is a poorly defined term that should be grouped with "other rhythms."

(14) Determine presence of bystander-CPR

This allows calculation of the percentage of cardiac arrests in which bystanders have initiated CPR. A high percentage of early bystander-initiated CPR effort is associated with improved survival from cardiac arrest. These data also provide audit data on the "chain of survival" within an emergency system and they are important for programme evaluation.

(15) Return of spontaneous circulation (ROSC)

The Utstein template accepts return of any spontaneous palpable pulse and requires no specific duration as a determinant. A palpable pulse in a major artery, usually the carotid artery, implies a systolic blood pressure of approximately 60 mm Hg. ROSC is clearly an intermediate outcome which may be evanescent. While it is of less clinical importance than hospital admission or eventual discharge, it may prove useful in clinical trials and other intervention studies.

(18) Admitted to hospital unit

This level of the template refers to patients who had ROSC sustained long enough to merit admission to the intensive care unit or another hospital unit. For the purposes of standardisation a successful hospital admission can relate only to a patient with spontaneous circulation and a measurable blood pressure with or without vasopressors. Patients may or may not be breathing spontaneously and they may or may not be intubated. The need for continuing CPR or mechanical CPR devices implies the absence of spontaneous circulation and such patients should be excluded. Artificial circulatory assists, such as emergency cardiopulmonary bypass and intra-aortic balloon pumps, imply that spontaneous circulation is present, and such patients should be included. The recommendations place no duration requirement on "successful admission." Ideally, however, a special note should be made of those patients

Outcome of brain injury: Glasgow-Pittsburgh cerebral performance and overall performance categories[7,8]

Cerebral performance categories	*Overall performance categories*
1 Good cerebral performance. Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities)	1 Good overall performance. Healthy, alert, capable of normal life. Good cerebral performance (CPC 1) plus no or only mild functional disability from noncerebral organ system abnormalities.
2 Moderate cerebral disability. Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, travelling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes	2 Moderate overall disability. Conscious. Moderate cerebral disability alone (CPC 2) or moderate disability from noncerebral system dysfunction alone or both. Performs independent activities of daily life (dressing, travelling, and food preparation). May be able to work part-time in sheltered environment but disabled for competitive work.
3 Severe cerebral disability. Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome	3 Severe overall disability. Conscious. Severe cerebral disability alone (CPC 3) or severe disability from non-cerebral organ system dysfunction alone or both. Dependent on others for daily support.
4 Coma, vegetative state. Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment	4 Same as CPC 4.
5 Death. Certified brain dead or dead by traditional criteria.	5 Same as CPC 5.

CPC, cerebral performance categories.

who die within the first 24 hours of admission. Patients who experience additional cardiac arrests during the index hospital admission are counted as a single person in the data analysis, whether or not they are successively resuscitated.

(20) Discharged alive

Reports should note the number of patients discharged from the hospital alive, and the discharge destinations: for example, home, pre-arrest residence, rehabilitation facility, extended care facility (nursing home), or other hospital. If possible and practical, researchers should record the "best-ever achieved" cerebral performance category (CPC) and overall performance category (OPC)[7,8] (see table). If "best-ever achieved" presents collection diffulties researchers should note the OPC and CPC at the time of discharge.

(22) Alive at one year

For those patients who survive for more than one years note the OPC and CPC near the one year mark. As core data, record the date and cause if death occurs in the first year after discharge. This allows calculation of length of survival. The recommendation relating to people who experience additional *out-of-hospital* cardiac arrests during their first year of survival is to treat each cardiac arrest and resuscitation attempt as a separate event. Thus a second cardiac arrest in the year after the index cardiac arrest marks the end of survival for the index event and counts as a "death" regardless of whether the person survived or not. If emergency personnel attempted to resuscitate this person in the later event, the template would count that person as an additional "resuscitation attempted". If they lived to hospital discharge again, they would continue to be counted as a completely separate person.

IV Time points and time intervals

Delay to treatment (especially the interval from collapse to the start of resuscitation efforts) determines the immediate, intermediate, and overall outcomes in cardiac arrest. All research into cardiac arrest and all evaluations of system performance depend on accurate recording of the time of specific events and the intervals between them. These key components warrant great emphasis in any research or system evaluation and systematic recording of event times should be delegated to a recognised member of the team. As such it should figure prominently in training and testing of personnel. Training in bystander CPR should emphasise the need to note when witnessed arrests occur and when basic CPR was started. Researchers should aim for as much precision as possible in recording time events. The key times as they relate to the patient, the dispatch centre, the ambulance, and the hospital are shown schematically in fig 3 as the four clocks of sudden cardiac arrest.

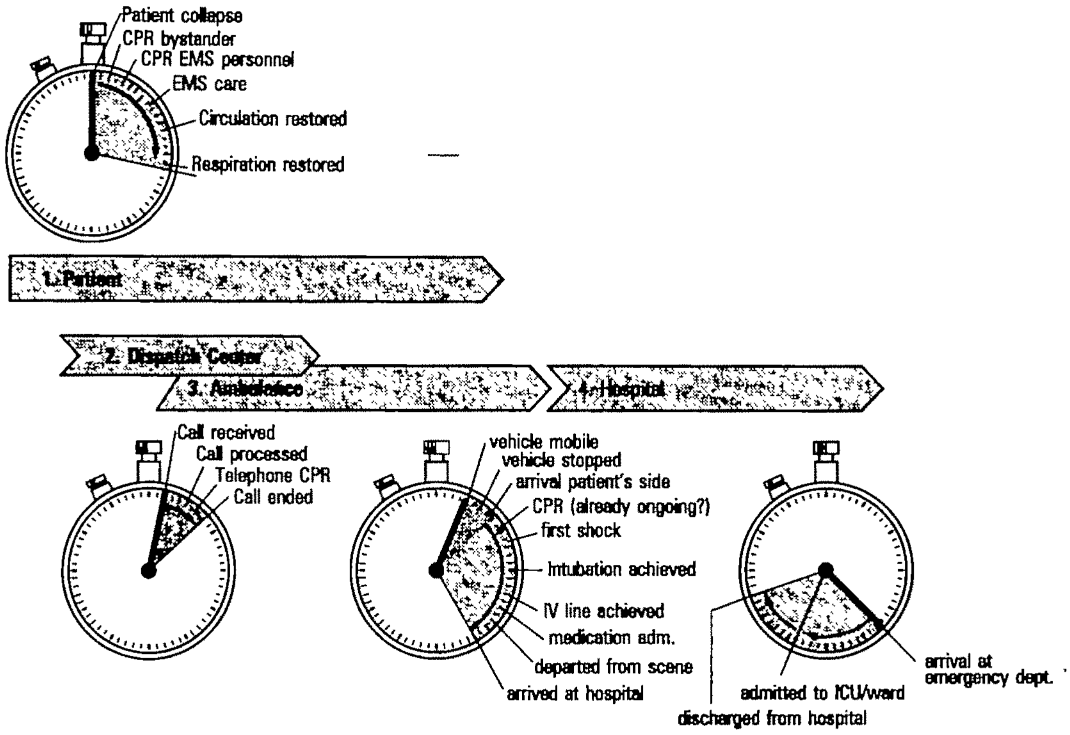
Figure 4 shows the major events that should be recorded for resuscitation attempts after cardiac arrest. The period between two time events is the "event-to-event" interval. Researchers should always use the term "interval" and not "time" to refer to the duration between any two events. The label for the interval should include the two index events. The "stacked index card" design of fig 4 denotes that these events can be shuffled, with events occurring in varying sequences with different patients.

Recording the times of events depicted in fig 4 permits many intervals to be calculated. Many of these, such as the interval from time of call to arrival at the patient's side are necessary for quality assurance and system evaluation. The two most important intervals from the perspective of patient survival, however, are those from collapse to first CPR attempt and from collapse to first defibrillatory shock.

CONFERENCE RECOMMENDATIONS FOR THE CORE TIME EVENTS TO BE RECORDED

Time of collapse/time of recognition Though it is classed as core information, imprecision surrounds the estimated time of collapse. The emergency personnel must ask additional

Figure 3 The four clocks of sudden cardiac arrest.



questions of the bystanders to obtain a best estimate. This information is crucial, however, for calculation of the approximate ischaemic interval. Note that time of collapse can be obtained only for witnessed cardiac arrests, for which the collapse or signs of distress are seen (or heard). Time of recognition refers to the time at which an unwitnessed arrest is discovered.

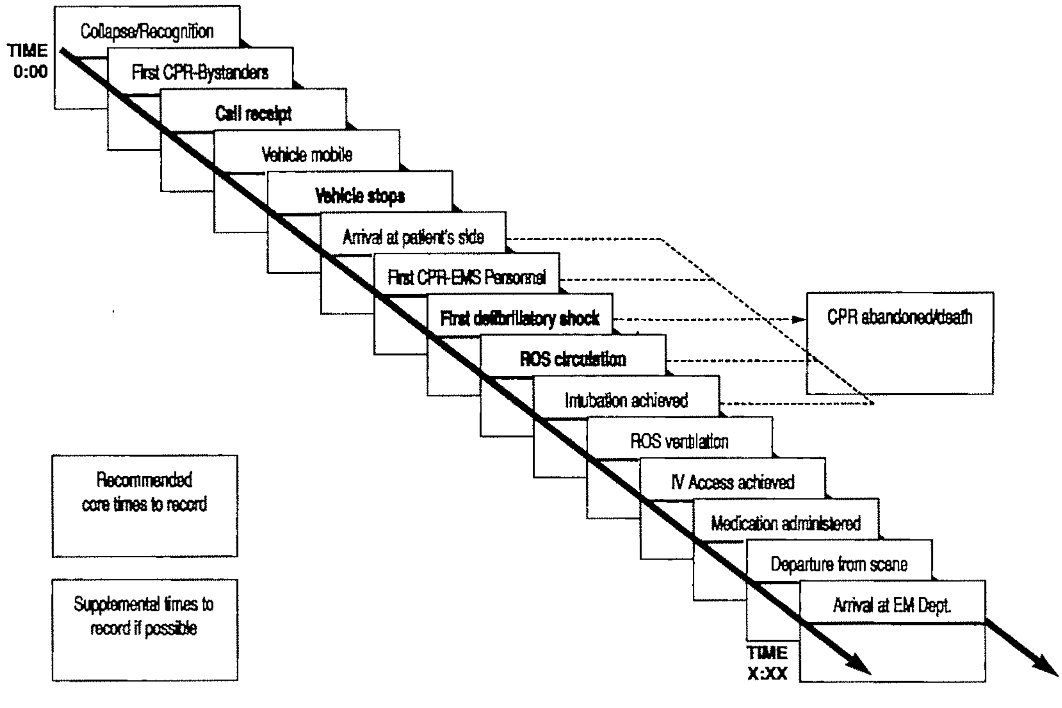
Time of call receipt Modern emergency dispatching systems record this event automatically. If multiple routings of the message occur, passing the call from dispatcher to dispatcher, the first contact gives the time of call receipt.

Time vehicle stops This is the time when the emergency response vehicle stops moving, at a location as close as possible to the patient. This replaces the commonly used term "time of arrival at scene", an imprecise term which may mean anything from destination in sight to personnel at patient's side.

Time of first CPR attempts The time of first CPR attempts should be recorded both for CPR initiated by bystanders and for CPR initiated by emergency personnel. Note in fig 4 that personnel should also record the time when further CPR is considered futile and they cease performing chest compressions and ventilations. While in general this would be the time of death, some systems require that a physician officially pronounce death which cannot be assumed until that moment.

Time of first defibrillatory shock Early

Figure 4 Events associated with out-of-hospital cardiac arrest resuscitation attempts.



defibrillation is the cornerstone for successful resuscitation of patients in ventricular fibrillation. The need to record accurately the time of delivery of the first shock must be emphasised. The interval from collapse to the first defibrillatory shock serves as a yardstick for other components of an emergency system because it is influenced by many variables: the competence of bystanders to recognise a cardiac arrest and respond appropriately, the efficiency of the dispatch system that can process calls quickly, and the skills of early defibrillation units that can gain access to the patient and perform their protocols rapidly. The best method to obtain this information is through automated external defibrillators or through conventional defibrillators with automated event documentation. These devices provide details automatically and accurately on initial rhythm, times, and the responses of heart rhythm to treatment. The use of devices with these capabilities must be encouraged.

Time of return of spontaneous circulation The importance of this event is self evident, but the need to make the appropriate observation must be emphasised.

Time CPR abandoned/death Emergency personnel should record the time at which they terminate resuscitation efforts outside the hospital.

Departure from scene and Arrival at the Emergency Department Although not strictly core data, emergency personnel can record these times easily and accurately. Related intervals are key components for an effective quality assurance and general management programme.

OTHER TIMES AND INTERVALS

Other important times are shown in fig 4. Wherever possible, these data should be collected, but they are accepted as having a somewhat lower priority for recording than the core items mentioned above. The new nomenclature for one interval should, however, be emphasised:

Call-response interval This term replaces "response time," one of the most frequently, and yet inconsistently, used terms in resuscitation. It is the period from receipt of call by the emergency response dispatchers to the moment when the emergency response vehicle stops moving. The call-response interval will therefore include the time required for processing the call, dispatching the emergency personnel, and the interval required for travel to the scene. Note that this interval does not extend to arrival at the patient's side nor to the time of defibrillation. Recent published data show that the additional intervals from when the vehicle stops to the moment of arrival at the patient's side and to the delivery of the first defibrillatory shock may be excessively long and may have a major role in determining survival.

V Collection of individual clinical data

Clinical outcomes Clinical outcome after attempted resuscitations comprises core information required for system evaluation and comparison and for evaluation of clinical trials. The chief goal of cardiopulmonary-cerebral resuscitation is to return victims to their pre-arrest level of neurological function. An evaluation of resuscitation efforts cannot be complete without assessment of neurological outcome in terms of both *quality* and *duration* of survival. Elaborate efforts at improving survival from cardiac arrest may produce greater numbers for only a short time and at a cost of more disability. This situation, were it to obtain, must be recognised.

The Glasgow-Pittsburgh outcome categories have become the most widely used methods of evaluating quality of life after successful resuscitation from cardiac arrest. The categories distinguish between the cerebral effects of the cardiac arrest and the morbidity of underlying, non-cerebral problems. The overall performance category (OPC) reflects cerebral plus non-cerebral status and evaluates general performance. The cerebral performance category (CPC) evaluates only cerebral performance capabilities. These outcome categories are reliable and easy to obtain. The Utstein consensus conference recommended use of the Glasgow-Pittsburgh outcome categories to record pre-arrest status, status at the time of discharge, and status after one year survival. Details are given in the table.

A single data collection form Many experts recommend the development of a single form for data collection that could be used in all emergency systems. Such a form would allow shared databases and patient registries and true multi-centre studies. We believe this to be impractical. We do recommend, however, that the data collection forms used by all systems provide the core data that will allow completion of the clinical portions of the Utstein template.

Recommended clinical data The Utstein Consensus Conference recommended that responsible personnel should attempt to record the clinical data listed below for each attempted resuscitation (an asterisk indicates core data):

- *Location of person's arrest**—home, street, public place, work place, mass gatherings, in the ambulance, nursing home, or other long-term care facility.
- *Pre-arrest clinical status*—overall performance category (OPC) and the cerebral performance category (CPC).
- *Witnessed arrest before arrival of emergency personnel**—state yes or no.
- *Precipitating insult*—acute cardiac event, trauma, exsanguination, hypoxia, intracranial event, intoxication (drug ingestion), metabolic, drowning, sepsis, sudden infant death syndrome. As core data, an attempt should be made at least to classify the arrest as "cardiac", or "non-cardiac"*.
- *Clinical status of patient when ambulance arrives**—breathing (yes/no), palpable pulse (yes/no), bystander-CPR (yes/no).
- *Arrest after arrival of emergency personnel*—yes or no.
- *Initial recorded rhythm*—ventricular fibrillation, ventricular tachycardia, asystole, and other.
- *Treatment*—The specific protocols used by a system should be listed when the emergency medical system is described. For individual patients, however, personnel should record the specific interventions they used. As core information, the personnel should record: the type of respiratory support provided (mouth to mouth or mask breathing, endotracheal intubation, other type of airway management), whether the intubation was successful, the number of defibrillatory shocks given, and the medications administered. The strong associa-

tion between unsuccessful resuscitation attempts and numerous interventions is obvious—the more difficult a resuscitation the more interventions that are used. Consequently, an account of interventions in unsuccessful attempts provides little information of value. Researchers must emphasise, therefore, all the interventions used for people who regained a spontaneous circulation.

- *Final patient status at the scene*—This refers to the condition of the patient when either transport starts or efforts end. The recommended categories are ROSC, continuing CPR, or death.
- *Status on arrival at emergency department*—This information would reflect a change in status during transport. The possibilities here are continuing CPR, pronounced dead on arrival (record specific time), or the presence of spontaneous circulation (ROSC). If the ROSC lasts more than five minutes, personnel should record the blood pressure, respiratory rate, and the Glasgow coma score. In addition, the personnel should record the patient's temperature, especially in arrests associated with hypothermia.
- *Status after treatment in the emergency department*—The possibilities are admission to the hospital intensive care unit or alternative location or "pronounced dead with termination of efforts".
- *Status on admission to hospital unit*—Personnel should record the Glasgow coma score, the blood pressure, the rate of spontaneous respirations, if any, and basic brain stem reflexes.
- *Discharged alive*—If the patient died in the hospital, personnel should record the time and date of death and the length of survival after ROSC. They should note those patients who die within 24 hours and the time at which death occurred. They should also record the overall performance category (OPC) and cerebral performance category (CPC) at time of discharge. If the person dies before surviving one year then record the best score achieved in the week before death. The supplementary data to record would include the "best-ever" outcome achieved during hospital admission and in the year after the arrest, though these data may be difficult to gather consistently.
- *Discharge destination*—If the patient is discharged, researchers should record the discharge destination: home (or pre-arrest residence), rehabilitation facility, extended care facility (nursing home), or other.
- *Alive at one year (yes or no)*—If yes, then record the OPC and CPC score at one year. Personnel can often obtain these scores via telephone interviews with family members. If the person dies in the first year, then record the date of death and the length of survival. Supplementary data would include the best CPC achieved before death.

VI Description of emergency systems

The organisation of a community's emergency medical services systems has a major effect on the outcome of cardiac arrest. Researchers should describe the dispatch component of an emergency system as well as the various response tiers. These descriptions should state *who* is in each tier, *what* interventions and actions they provide, *how* (and *how well*) they provide those interventions, and *when* they deliver their care. While it would be impractical to report all of these details in every publication, authors should aim to provide as many of the recommended core data as possible.

(A) THE DISPATCH SYSTEM

Describe the dispatch system in terms of whether it is dedicated to emergency medical services only or whether the dispatch system must also cover fire and police. State the type of communication system used—such as 911 or 999. Give the median interval for dispatch call-processing, defined as the time from the call is first received to when the emergency vehicle is moving.

(B) FIRST TIER: THE FIRST EMERGENCY PERSONNEL TO ARRIVE

Who The personnel in the first tier should be described (physicians, nurses, ambulancemen, emergency medical technicians, first responders). State the organisational affiliation of the personnel in terms of dedicated emergency service, mixed EMS-fire service, hospital-based, private ambulance company, or other. Describe the following features: total number of personnel in this tier, status (paid *v* volunteer), number of hours of training, number of team members per response unit, number of vehicles in service at a given time, number of responses/community/year.

What Describe the major interventions permitted for use in cardiac resuscitation. In broad categories these include CPR, defibrillatory shocks, intravenous medications, and technical airway management.

How Describe the general resuscitation protocols in terms of sequence and type of intervention. State whether protocols adhere to those recommended by a recognised group such as the American Heart Association or the European Resuscitation Council. Describe whether personnel follow standing orders or whether they must obtain radio or telephone permission before initiation of treatment. State whether the emergency system permits field personnel to cease resuscitation efforts in the field.

When Describe the median (not mean) call response interval for the various tiers of the response system.

SECOND AND THIRD TIERS

In most locations in the United States paramedical staff are the second tier of emergency personnel to arrive and there is no third tier. In Europe there is often a second or third tier that consists of emergency physicians who respond outside the hospital. Reports must describe these additional tiers in the same detail and by the same features as noted above for the first responding tier.

Discussion

Standardisation of nomenclature should facilitate audit and comparative studies for existing practices and also should aid the evaluation of developments in emergency cardiac care. For example, system directors will need to know the relative merits of automated external defibrillators and conventional defibrillators, but studies in single centres may be inadequate to provide reliable information. Managers and medical directors in both the United States and Europe have even started to examine the economic effects of the widespread use of systems manned by paramedical staff. They wish to determine whether these services produce enough clinical benefit to justify their cost. A trend in the opposite direction has been triggered by unemployment of physicians in some parts of the world. This engenders a reluctance to delegate skills such as defibrillation and intubation to non-physicians. Only the steady accumulation of valid research using similar vocabularies and comparable data can determine the relative merits of different systems.

Several other benefits will follow the use of uniform terminology and clinical variables. These include better evidence on the epidemiology of cardiac arrest, the identification of special high risk subgroups, the factors that determine survival, and the specific interventions that reduce mortality. Areas of research for single or multicentre studies may include: the efficacy of drug treatment, new system strategies such as widespread first responder defibrillation, and the value of widespread public education relating to the early recognition, and first aid management of cardiac pain and cardiac arrest.

The concept of a consensus conference to standardise format and nomenclature for biomedical journals has precedents. For example, the recommendations of a group of biomedical journal editors who met in Vancouver, British Columbia, in 1978 have come to be known as the "Vancouver style". They formed an international committee of medical journal editors which has published a series of updates since then. The Utstein Consensus Task Force recognises, that with use, certain features of the Utstein guidelines will also need to be revised and broadened.

The Utstein consensus conferences were supported by a grant from the Laerdal Foundation for Acute Medicine.

1 Special report: Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991;84:960–75.

2 Task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein Style. *Ann Emerg Med* 1991;20:861–74.

3 Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the "Utstein style". Prepared by a task force of representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. *Resuscitation* 1991;22:1–26.

4 Der "Utstein-Style". Die Mitglieder einer Arbeitsgruppe der American Heart Association des European Resuscitation Council, der Heart and Stroke Foundation of Canada, des Australian Resuscitation Council. *Notfallmedizin* 1991;17:510–8, 626–35, 670–5.

5 Der "Utstein-Style". Die Mitglieder einer Arbeitsgruppe der American Heart Association des European Resuscitation Council, der Heart and Stroke Foundation of Canada, des Australian Resuscitation Council. *Intensivmedizin und Notfallmedizin*. 1992 (in press).

6 Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest (new abridged version). The "Utstein Style". *Eur J Anaesthesiol* 1992;9:185–(in press).

7 Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet* 1975;1:480–4.

8 Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods, and patient characteristics. *Am J Emerg Med* 1986;4:72–86.

Br Heart J 1992;67:334–8

Mortality within hospital after resuscitation from ventricular fibrillation outside hospital

William Dickey, A A Jennifer Adgey

Abstract

Objective—**To determine factors related to mortality within hospital after successful resuscitation from ventricular fibrillation outside hospital by a mobile coronary care unit manned by a physician.**

Design—**Retrospective review of records of patients resuscitated and admitted to hospital between 1 January 1966 and 31 December 1987.**

Setting—**Mobile coronary care unit, coronary care unit, and cardiology department.**

Patients—**281 patients (227 male), aged 14–82 (mean 58) successfully resuscitated from ventricular fibrillation outside hospital of whom 182 (65%) developed ventricular fibrillation before the arrival of the mobile coronary care unit. The aetiology of ventricular fibrillation was acute myocardial infarction in 194 patients (69%), ischaemic heart disease without infarction in 71 (25%), and other or unknown in 16 (6%).**

Main outcome measures—**Death within hospital.**

Results—**There were 91 deaths in hospital (32%). Factors on univariate analysis significantly associated with increased mortality were patient age ≥60 years, previous myocardial infarction or cerebrovascular disease, prior digoxin or diuretic treatment, collapse without prior chest pain or with pain lasting 30 minutes or less, defibrillation delayed by ≥5 min, ≥four shocks required to correct ventricular fibrillation, left ventricular failure or pulmonary oedema and cardiogenic shock after successful defibrillation, and coma on admission to hospital. On multivariate analysis the most important factors (in rank order) were cardiogenic shock after defibrillation, coma on admission to hospital, age ≥60 years and the requirement for four or more shocks to correct ventricular fibrillation.**

Conclusions—**The in-hospital mortality of patients resuscitated from ventricular fibrillation outside hospital was related to patient characteristics before the cardiac arrest and to the immediate haemodynamic and neurological status after correction of ventricular fibrillation as well as to factors at the resuscitation itself. The in-hospital mortality of this study compares favourably with the results obtained by units staffed by paramedical workers and emergency medical technicians, although 35% (99/281) of the patients had ventricular fibrillation after the arrival of the mobile unit and defibrillation was thus rapid.**

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Since the feasibility of resuscitation from ventricular fibrillation outside hospital was first demonstrated in Belfast in 1966,[1] many mobile coronary care schemes have been established. In the United States there are now more than 300 prehospital coronary care programmes.[2] Of the many published studies of outcome after prehospital cardiac arrest, most have concentrated on the relation between resuscitation-related factors (such as availability of bystander cardiopulmonary resuscitation and delay in defibrillation) and survival rather than patient characteristics before the arrest or haemodynamic status after correction of ventricular fibrillation. Furthermore, few studies have considered factors specifically related to death within hospital for patients who survive to be admitted. We describe 281 patients resuscitated from ventricular fibrillation outside hospital by the Royal Victoria Hospital's mobile coronary care unit and we assess factors related to in-hospital mortality.

Patients and methods

PATIENTS

We studied patients who were resuscitated outside hospital after ventricular fibrillation developed and who were admitted to hospital by the Royal Victoria Hospital mobile coronary care unit between 1 January 1966 and 31 December 1987. Patients developed ventricular fibrillation before or after the arrival of the mobile unit. When ventricular fibrillation developed after the mobile unit's arrival, patients received immediate defibrillation. Patients were not included in the study if ventricular fibrillation was iatrogenic—that is, if it occurred during treatment of ventricular tachycardia or asystole.

COLLECTION OF DATA

Since the mobile unit started operation, patient characteristics, circumstances of arrest, resuscitation details, and condition after successful resuscitation have been recorded on standardised forms. The following factors were studied to determine their relevance to outcome:

Patient characteristics—sex, age, previous history of myocardial infarction, previous stable angina or chronic cardiac dyspnoea (New York Heart Association grade II or greater), previous hypertension, diabetes mellitus or cerebrovascular event (stroke or transient ischaemic attack), previous drug treatment (digoxin, diuretics, β blocking and antiarrhythmic agents), smoking history.

Aetiology and circumstances of arrest—aetiology, site of infarction if present, year, time, place, ventricular fibrillation before or after the arrival of the mobile unit, presence or absence of chest pain and its duration before ventricular fibrillation.

Resuscitation details—presence or absence of cardiopulmonary resuscitation before defibrillation, cardiopulmonary resuscitation operator, delay in starting cardiopulmonary resuscitation after collapse where given, delay in defibrillation, number of shocks required to correct ventricular fibrillation (defined as the total number of shocks administered at the time of the initial arrest outside hospital before a stable rhythm was achieved and maintained even if ventricular fibrillation recurred after the initial resuscitation at the time of the initial arrest).

Condition after successful defibrillation—left ventricular failure or pulmonary oedema, cardiogenic shock (systolic blood pressure < 80 mm Hg with peripheral circulatory shutdown), coma on admission to hospital.

Statistical analysis was performed with the *Statistical Package for the Social Sciences-II* program on a Digital Professional 350 microcomputer. To test single factors for significance in influencing in-hospital mortality we used a χ^2 test with Yates's correction on 2 × 2 contingency tables. We used the multiple regression program of *Statistical Package for the Social Sciences-II* for multivariate analysis in order to determine the most significant factors and rank them in order.

Results

PATIENTS

Between 1 January 1966 and 31 December 1987, 281 patients (227 male; age range 14–82; mean (1 SD) 58 (12) years) in whom ventricular fibrillation developed outside hospital were successfully resuscitated by the Royal Victoria Hospital mobile coronary care unit and were admitted to hospital. The cardiac arrest was witnessed in all except one patient. One hundred and eighty two (65%) patients developed ventricular fibrillation before the arrival of the mobile unit.

AETIOLOGY

The aetiology of ventricular fibrillation was identified as acute myocardial infarction on the basis of electrocardiograph and/or serial cardiac enzyme changes in 194 (69%) patients. The site of infarction was inferior or posterior in 66 patients (34%), anterior in 121 (62%), and was unknown in seven (4%). Seventy one (25%) of the 281 patients had ischaemic heart disease but no evidence of acute myocardial infarction at the time of ventricular fibrillation. Thus coronary artery disease, with or without acute myocardial infarction, caused ventricular fibrillation in 265 (94%) of the patients seen. The aetiology was not related to coronary artery disease in 13 patients and was unknown in three.

IN-HOSPITAL MORTALITY

Of the 281 patients, 91 (32%) died in hospital; thus 190 patients (68%) survived to be discharged. Of the 91 in-hospital deaths, 41 (45%) occurred within 48 hours of the initial arrest and 50 (55%) occurred ⩾48 hours later. Death was due to intractable ventricular fibrillation (23 patients), cerebral anoxia (24), cardiogenic shock (nine), respiratory failure (13), cardiac failure (17), and bradyasystole (five).

FACTORS RELATED TO IN-HOSPITAL MORTALITY AND SURVIVAL TO DISCHARGE

Patient characteristics

Patients who survived to leave hospital were significantly younger (56·0 (12)) than those who died before discharge (60·8 (11)) ($p < 0.01$).

Table 1 Patient characteristics significantly associated with in-hospital mortality (univariate analysis) (%)

Factor	*Survived*	*Died*	χ^2	*DF*	*Significance*
Age:					
<40	11 (85)	2 (15)	11·46	2	0·01 > p > 0·001
⩾40–<60	104 (76)	32 (24)			
⩾60	75 (57)	57 (43)			
Previous MI*:					
Yes	73 (61)	47 (39)	4·20	1	0·05 > p > 0·01
No	117 (73)	43 (27)			
Previous cerebrovascular event†:					
Yes	5 (33)	10 (67)	7·44	1	0·01 > p > 0·001
No	184 (70)	77 (30)			
Prior digoxin therapy‡:					
Yes	20 (53)	18 (47)	3·99	1	0·05 > p > 0·01
No	169 (70)	71 (30)			
Prior diuretic therapy‡:					
Yes	38 (55)	31 (45)	6·26	1	0·05 > p > 0·01
No	151 (72)	58 (28)			

DF, degrees of freedom, MI, myocardial infarction.
*One missing observation, †five missing observations, ‡three missing observations.

Table 2 Factors related to the cardiac arrest that were significantly associated with in-hospital mortality (univariate analysis) (%)

Factor	*Survived*	*Died*	χ^2	*DF*	*Significance*
VF before arrival of mobile unit:					
Yes	112 (62)	70 (38)	7·94	1	$0.01 > p > 0.001$
No	78 (79)	21 (21)			
Chest pain before VF:					
Yes	136 (72)	53 (28)	4·38	1	$0.05 > p > 0.01$
No	54 (59)	38 (41)			
Duration of chest pain before VF:					
$\leqslant 30$ min	16 (53)	14 (47)	6·47	2	$0.05 > p > 0.01$
>30 min <4 h	106 (76)	33 (24)			
$\geqslant 4$ h	14 (70)	6 (30)			
Delay in defibrillation*:					
<5 min	106 (75)	36 (25)	6·00	2	$0.05 > p > 0.01$
5–9 min	38 (62)	23 (38)			
$\geqslant 10$ min	45 (60)	30 (40)			
Shocks to correct VF(n)*:					
<4	138 (72)	53 (28)	5·31	1	$0.05 > p > 0.01$
$\geqslant 4$	50 (57)	37 (43)			

DF, degrees of freedom; VF, ventricular fibrillation.
*Three missing observations.

The influence of patient age on survival to leave hospital was confirmed by χ^2 testing (table 1). Single-factor analysis showed that the following patient characteristics were also significantly ($p < 0.05$) associated with in-hospital mortality: previous myocardial infarction, previous cerebrovascular event, prior digoxin therapy, and prior diuretic therapy.

Aetiology and circumstances of arrest

Single factor analysis showed that the following circumstances of the cardiac arrest were significantly associated with death in hospital (table 2): ventricular fibrillation developing before the arrival of the mobile unit, collapse without preceding chest pain, pain lasting $\leqslant 30$ minutes before collapse for patients who had chest pain, delay in defibrillation $\geqslant 5$ minutes after collapse, and the requirement for four or more shocks to correct ventricular fibrillation at the initial arrest and to allow a stable rhythm to be maintained.

Condition after successful defibrillation

The presence of the following features after successful defibrillation was significantly related to in-hospital mortality on single factor analysis (table 3): left ventricular failure or pulmonary oedema, cardiogenic shock, and failure to recover consciousness by the time of admission to hospital.

Factors not related to outcome

These were sex, previous stable angina, previous chronic cardiac dyspnoea, history of hypertension, diabetes mellitus, prior treatment with β blockers or antiarrhythmic agents, a history of smoking, aetiology of ventricular fibrillation, site of infarct if ventricular fibrillation was caused by acute myocardial infarction, year, time and place of ventricular fibrillation, presence or absence of cardiopulmonary resuscitation before defibrillation if patients had ventricular fibrillation before the arrival of the mobile unit, and for patients who received cardiopulmonary resuscitation, the delay to resuscitation and type of operator.

Multivariate analysis

Factors shown to be significantly related to in-hospital mortality on univariate analysis were also analysed by a stepwise forward algorithm with factors entered as binary variables.

Factors of greatest significance in predicting in-hospital mortality were cardiogenic shock after successful defibrillation, coma on admission to hospital, age $\geqslant 60$ years, and the need for four or more shocks to correct ventricular fibrillation (table 4).

Discussion

The initial experience with the Royal Victoria

Table 3 Factors after successful defibrillation significantly associated with in-hospital mortality (univariate analysis) (%)

Factor	*Survived*	*Died*	χ^2	*DF*	*Significance*
Cardiac failure*:					
No	127 (73)	48 (27)	11·33	2	$0.01 > p > 0.001$
Mild/moderate	52 (65)	28 (35)			
Pulmonary oedema	10 (40)	15 (60)			
Cardiogenic shock:					
Yes	1 (4)	24 (96)	47·58	1	$p < 0.001$
No	189 (74)	67 (26)			
Coma on hospital admission:					
Yes	65 (56)	51 (44)	11·22	1	$p < 0.001$
No	125 (76)	40 (24)			

*One missing observation. DF, degrees of freedom.

Table 4 Factors significantly ($p < 0·05$) related to in-hospital mortality on stepwise multiple regression analysis

Step	Factor	Standardised Coefficient	F value
1	Cardiogenic shock after defibrillation	0·443	70·62
2	Coma on hospital admission	0·181	10·73
3	Age ⩾60	0·138	6·88
4	⩾4 shocks to correct VF	0·112	4·16

VF, ventricular fibrillation.

Hospital mobile coronary care unit[3] confirmed that ventricular fibrillation was the usual rhythm of cardiac arrest in patients who were seen soon after collapse and that successful resuscitation and survival to leave hospital were practical propositions for patients who had ventricular fibrillation outside hospital.

Although there have been many subsequent reported studies of survival after pre-hospital cardiac arrest most have considered pre-hospital and in-hospital mortality together and few have specifically assessed deaths after hospital admission. Furthermore, most have concentrated on resuscitation details rather than on patient characteristics and haemodynamic status after correction of ventricular fibrillation.

PATIENTS STUDIED

The patients studied here differ in two major respects from those resuscitated out of hospital from ventricular fibrillation and cardiac arrest irrespective of rhythm by paramedical and emergency medical technician-based units. Firstly, 69% of all patients and 73% of patients with coronary artery disease were identified as having had acute myocardial infarction at the time of ventricular fibrillation. In comparison, other studies have suggested that acute myocardial infarction or acute transmural myocardial infarction accounts for a minority of cases of cardiac arrest out of hospital, with figures of 17–40% for patients surviving to reach hospital[4–6] and in some cases to be discharged home.[4] Secondly, a higher proportion of patients (35%) developed cardiac arrest after the arrival of the mobile unit than in other studies (11–16%).[4 6 7] These features may reflect differences in the use of our unit, which was established to provide physician-based care not only in cases of sudden death but also to manage patients in the early phase of acute myocardial infarction.[8] Three quarters of patients resuscitated from cardiac arrest out of hospital by another physician-manned mobile unit based in Reykjavik had acute infarction.[9]

In our study the in-hospital mortalities of 32% for all patients and of 38% for patients who had ventricular fibrillation before the arrival of the unit compare favourably with results of 41–52% reported by units manned by paramedical staff and emergency medical technicians.[10–14] We showed no significant relation between in-hospital mortality and the aetiology of ventricular fibrillation.

FACTORS RELATED TO IN-HOSPITAL MORTALITY

Patient characteristics

The importance of age in relation to death within hospital was confirmed both on univariate and on multivariate analysis, where on stepwise analysis it appeared after cardiogenic shock and coma following defibrillation. Other studies have confirmed the association of patient age and outcome within hospital after resuscitation from out-of-hospital ventricular fibrillation and other cardiac arrest rhythms.[15–17]

Of other patient characteristics, previous history of myocardial infarction, cerebrovascular event, and prior digoxin or diuretic therapy were associated with increased in-hospital mortality. Few studies have assessed any of these factors. Weaver *et al* did not find prior digoxin or diuretic therapy to be significantly related to in-hospital mortality after resuscitation from ventricular fibrillation out of hospital.[18] The increased in-hospital mortality associated with digoxin and diuretic therapy in the present study may reflect an increased likelihood of collapse without warning chest pain and hence delayed defibrillation. Alternatively, these drugs may be indicators of poor cardiac function. An increased in-hospital mortality for patients resuscitated from out of hospital ventricular fibrillation with a previous history of cardiac failure has been reported.[16]

Circumstances of cardiac arrest

Ventricular fibrillation occurring before the arrival of the mobile unit and defibrillation delayed by ⩾5 minutes were significantly associated with increased in-hospital mortality and confirm the importance of early defibrillation.[19] Further support is provided by the increased mortality in patients who collapsed without warning chest pain (and in whom, therefore, defibrillation must have been delayed) and in patients who had pain lasting ⩽30 minutes who because of delays in summoning help were more likely to have collapsed before the arrival of the mobile unit. The association between the number of shocks required to correct ventricular fibrillation and outcome was confirmed both on univariate and multivariate analysis. Dunn *et al* confirmed an increased in-hospital mortality for patients who require ⩾4 shocks to terminate in-hospital or out-of-hospital ventricular fibrillation,[20] and Hargarten *et al* showed a linear decrease in survival with each shock delivered (up to five) for patients receiving treatment for ventricular fibrillation outside hospital.[7]

Condition after successful defibrillation

Univariate analysis showed that left ventricular failure and cardiogenic shock after successful defibrillation were significant predictors of in-hospital mortality; and multivariate analysis showed cardiogenic shock to be the most important predictor of death in hospital. Few studies of patients resuscitated from ventricular fibrillation out of hospital have considered the influence of haemodynamic status after resuscitation on survival. Liberthson *et al* reported an in-hospital mortality of 92% for patients who had cardiogenic shock after resuscitation from ventricular fibrillation out of hospital and of 64% for patients with congestive heart failure compared with 58% for all patients.[5] Studies of ventricular fibrillation in hospital confirm the adverse influence of cardiac failure and cardiogenic shock at the time of ventricular fibrillation on in-hospital mortality.[21 22]

Unconsciousness on admission to hospital was a significant predictor of in-hospital mortality both on univariate and multivariate analysis. Again, the importance of early defibrillation in speeding neurological recovery and hence survival has been confirmed elsewhere.[23 24]

In conclusion, our results show that a favourable outcome for discharge from hospital after resuscitation from ventricular fibrillation out of hospital is more likely in young patients with no prior cardiac history who have immediate or early defibrillation, no haemodynamic abnormality, and who recover consciousness rapidly after correction of ventricular fibrillation. Wider availability of early defibrillation outside hospital particularly in the home, at work, and in public places by automatic, semi-automatic, and trans-telephonic defibrillators will increase the likelihood of survival after the onset of ventricular fibrillation outside hospital.

1 Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. *Lancet* 1967; ii:271–3.

2 Eisenberg MS, Bergner L, Hearne T. Out-of-hospital cardiac arrest: a review of major studies and a proposed uniform reporting system. *Am J Public Health* 1980;70:236–40.

3 Adgey AAJ, Nelson PG, Scott ME, Geddes JS, Allen JD, Zaidi SA, *et al.* Management of ventricular fibrillation outside hospital. *Lancet* 1969;i:1169–71.

4 Baum RS, Alvarez H, Cobb LA. Survival after resuscitation from out-of-hospital ventricular fibrillation. *Circulation* 1974;50:1231–5.

5 Liberthson RR, Nagel EL, Hirschmann JC, Nussenfeld SR. Prehospital ventricular defibrillation: prognosis and follow-up course. *N Engl J Med* 1974;291:317–21.

6 Goldstein S, Landis JR, Leighton R, Ritter G, Vasu CM, Wolfe RA, *et al.* Predictive survival models for resuscitated victims of out-of-hospital cardiac arrest with coronary heart disease. *Circulation* 1985;71:873–80.

7 Hargarten KM, Stueven HA, Waite EM, Olson DW, Mateer JR, Aufderheide TP, *et al.* Prehospital experience with defibrillation of coarse ventricular fibrillation: a ten-year review. *Ann Emerg Med* 1990;19:157–62.

8 Webb SW, Adgey AAJ, Pantridge JF. Autonomic disturbance at onset of acute myocardial infarction. *BMJ* 1972;iii:89–92.

9 Einarsson O, Jakobsson F, Sigurdsson G. Advanced cardiac life support in the pre-hospital setting: the Reykjavik experience. *J Intern Med* 1989;225:129–35.

10 Myerburg RJ, Conde CA, Sung RJ, Mayorga-Cortes A, Mallon SM, Sheps DS, *et al.* Clinical electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. *Am J Med* 1980;68:568–76.

11 Aprahamian C, Thompson BM, Gruchow HW, Mateer JR, Tucker JF, Stueven HA, *et al.* Decision making in prehospital sudden cardiac arrest. *Ann Emerg Med* 1986;15:445–9.

12 Stults KR, Brown DD, Kerber RE. Efficacy of an automated external defibrillator in the management of out-of-hospital cardiac arrest: validation of the diagnostic algorithm and initial clinical experience in a rural environment. *Circulation* 1986;73:701–9.

13 Cummins RO, Eisenberg MS, Litwin PE, Graves JR, Hearne TR, Hallstrom AP. Automatic external defibrillators used by emergency medical technicians: a controlled clinical trial. *JAMA* 1987;257:1605–10.

14 Weaver WD, Hill D, Fahrenbruch CE, Copass MK, Martin JS, Cobb LA, *et al.* Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest. *N Engl J Med* 1988;319:661–6.

15 Ritter G, Wolfe RA, Goldstein S, Landis JR, Vasu CM, Acheson A, *et al.* The effect of bystander CPR on survival of out-of-hospital cardiac arrest victims. *Am Heart J* 1985;110:932–7.

16 Hallstrom AP, Cobb LA, Swain M, Mensinger K. Predictors of hospital mortality after out-of-hospital cardiopulmonary resuscitation. *Crit Care Med* 1985;13:927–9.

17 Tresch DD, Thakur RK, Hoffmann RG, Olson D, Brooks HL. Should the elderly be resuscitated following out-of-hospital cardiac arrest? *Am J Med* 1989;86:145–50.

18 Weaver WD, Cobb LA, Hallstrom AP, Fahrenbruch C, Copass MK, Ray R. Factors influencing survival after out-of-hospital cardiac arrest. *J Am Coll Cardiol* 1986;7: 752–7.

19 Eisenberg MS, Hallstrom AP, Copass MK, Bergner L, Short F, Pierce J. Treatment of ventricular fibrillation: emergency medical technician defibrillation and paramedic services. *JAMA* 1984;251:1723–6.

20 Dunn HM, McComb JM, MacKenzie G, Adgey AAJ. Survival to leave hospital from ventricular fibrillation. *Am Heart J* 1986;112:745–51.

21 Lawrie DM, Higgins MR, Godman MJ, Oliver MF, Julian DG, Donald KW. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 1968;ii:523–8.

22 Dubois Ch, Smeets JP, Demoulin JCl, Piérard L, Foidart G, Henrard L, *et al.* Incidence, clinical significance and prognosis of ventricular fibrillation in the early phase of myocardial infarction. *Eur Heart J* 1986;7:945–51.

23 Weaver WD, Copass MK, Bufi D, Ray R, Hallstrom AP, Cobb LA. Improved neurologic recovery and survival after early defibrillation. *Circulation* 1984;69:943–8.

24 Longstreth WT, Inui TS, Cobb LA, Copass MK. Neurologic recovery after out-of-hospital cardiac arrest. *Ann Intern Med* 1983;98:588–92.

Br Heart J 1992;67:339–40

BRITISH CARDIAC SOCIETY NEWSLETTER

Registrar training

Implementation of the new pattern of training for registrars has been predictably slow. Cardiology is not the only specialty that is changing. All the major specialties are following our initiative in introducing three year blocks to replace the two year registrar and four year senior registrar posts. Many regional health authorities had only recently reorganised rotations on the old template when the new requirements became known, and the dismay was understandable from all who had worked hard to piece together a complex jigsaw. Now the process has had to start again. Problems are compounded by the necessary differences in training requirements. Cardiology has considerably more need for technical skills than most medical specialties, and only gastroenterology runs it close in this respect. Of our six year programme, we therefore require five to be centred on cardiology with only one in general internal medicine (that may, of course, be based principally on another subspecialty). Others require totals within their disciplines ranging from two to four. All require rotations between specialist centres and district general hospitals. Research has to be fitted into the formula with rules that have not yet been defined fully. The very large reduction in the number of career registrar posts imposed by the Joint Planning Advisory Committee (JPAC) could generate competition, claims, and counter claims between consultants who see a threat to their ability to provide a safe service—though all the meetings we have attended have been notable for the spirit of cooperation that has emerged. The difficulties that beset authorities struggling to satisfy as many as possible of the requirements and competing claims could very readily induce inertia born of helplessness. In this setting a sensible tactic encouraged by the Manpower Committee of the Royal College of Physicians is for a few regions to take a lead, with all the support that is necessary from both local and national representatives of the specialties. The North West Thames Region is amongst those furthest along the difficult path, and it now has draft proposals that have been under discussion since February. The North East Thames and Trent regions are close behind. Other regions have arranged many meetings and are likely to adopt some of the principles already worked out elsewhere.

General medical component in cardiology training

In addition to doubts about numbers of available posts, the criteria needed for district hospitals to take part in rotations, the arrangements to accommodate the different types of research, and the special requirements of high flying academics, cardiology faces one more issue that has not yet been settled—though a decision is needed urgently. The Specialty Advisory Committee in General Internal Medicine requires at present that our trainees spend one year in Internal Medicine *at senior registrar level* if dual accreditation is to be granted. This has been assumed to translate into one year of the new final three year block. But this is disruptive for major centres and unsettling for trainees particularly for those with interventional skills that have to be maintained and fine tuned. It also adds to the difficulty of establishing rotations within the first three years: inclusion of general medicine here makes the jigsaw appreciably easier. The proposal has been made recently that the general medical year could be the last of the first three year block—still within four years of the end of the training programme, as now. We hope this compromise will be acceptable, for without it we may have to revert to single accreditation for at least some of our trainees. We would regard this as a retrograde step, especially with the increasing emphasis on cardiology in the district hospitals.

Cardiology in the district hospital

A Working Party of the British Cardiac Society on Cardiology in the District Hospital reported in 1987. We intended that the report should be updated from time to time. This is now opportune because of the major changes that are occurring both in the practice of the specialty and in the organisation of health services generally. Council believe that an entirely new team will find it easier to take a fresh look at an evolving scene. They emphasised that this decision implied no dissatisfaction with the previous group: at least one of the authors of your Newsletter (who was Chairman of the previous Working Party) hopes that this sentiment is sincere . . . The chairman of the new group will be Andrew McLeod: membership will be announced in due course.

Coronary prevention working party

As a result of helpful advice from Michael Oliver, Council has decided to postpone plans for an update of the British Cardiac Society report on coronary disease prevention. One meeting of the group has already taken place, so the change of plan was not made lightly. But two factors led us to this decision. First, a number of doubts about the long-term value of some measures of primary prevention will not be fully resolved for at least a couple of years. Secondly, several other reports will be published in the next 12 months, and it may be unwise to confuse the public with a plethora of advice that may seem to differ in emphasis. Plans for a new report have not been abandoned. It is only the timing that has changed.

Campaign for legislation on smoking

Andrew McLeod has another special responsibility on Council. He maintains an interest on our behalf in the campaign against smoking. He has sent the following note for the newsletter.

"Thoracic physicians have taken the initiative in forming Doctors for Tobacco Law. As cardiologists, we have been urged to support them in achieving a higher profile for clinicians who seek to influence politicians in the battle to reduce smoking prevalence. As part of this campaign, each of us should consider writing to our local Member of Parliament to request support for the initiative of the European Community directive aimed at banning tobacco advertising and sponsorship. Our Government are at present taking a weak line on this issue. Yet advertising bans in New Zealand and Canada have been followed by a reduction in cigarette consumption. Informed advice suggests that the Government is nonetheless sensitive to consumer and constituency opinion on this issue. Do not delay. Write to your Member of Parliament at the House of Commons now." Council warmly endorses this advice.

Survivors of myocardial infarction and patients with stable angina: research initiatives

David de Bono, John Hampton, and Bob Wilcox have also written to the newsletter regarding two possible new trials that will interest members of the society. They pose important questions and suggest how we could find answers. "When should we advise coronary angiography for patients with 'stable' angina or for the survivors of recent myocardial infarction, whether or not they have had thrombolysis? While we may accept that left ventricular function and the distribution of coronary lesions helps us to stratify patients by risk, how certain are we that intervention (CABG, PTCA) based on angiographic findings is beneficial in such patients? Current medical opinion is divided on the best way to investigate and manage patients with stable angina pectoris whose symptoms are controlled on medical therapy. Is knowledge of the specific coronary anatomy in an individual patient essential for optimal planning or can angiography be deferred until required on symptomatic grounds? We may accept that most survivors of acute infarction should be given the opportunity of tolerating β blockers and/or aspirin, but the place of angiography is by no means established from good prospective trials. Further, the policy of post-infarct exercise testing is widespread, yet we have no clear guidelines of when, how much, or what precisely to do with those who have a "positive" result. These questions have enormous implications for resource planning and training. In some areas the waiting time for diagnostic angiography and surgery for symptomatic patients may exceed twelve months, even without the added workload imposed by a policy of "exposing ischaemia" in those who are symptomatically well. We are therefore proposing two prospective randomised trials. We plan to call them CAMI (Coronary Angiography after Myocardial Infarction) and CASA (Coronary Angiography in Stable Angina). In brief, patients with positive exercise tests (still to be defined) will be randomised to be offered angiography or not. The former will be advised to proceed to intervention according to predetermined anatomical distributions of their coronary lesion(s) whereas the latter will be offered angiography according to subsequent symptoms. Patients who have negative stress tests (and therefore would not qualify anyway for randomisation) and those randomised to angiography who decline to have it will also be followed up. We wish to determine whether a policy of symptomatic treatment, with angiography as necessary, is less, the same, or more 'advantageous' than a policy of early investigation and intervention. We will be interested in comparing the demand for intervention of an early versus a deferred investigational policy, the subsequent clinical course of the different patient groups (symptoms, quality of life, medical therapy, readmissions, re-infarctions), and survival. If you, too, feel that the answers to these questions are important why not join us?" Those interested should write to Bob Wilcox at the Department of Cardiovascular Medicine, University Hospital, Nottingham NG7 2UH.

The Harrogate meeting

We have a last report on plans for our spring meeting (26 May–29 May). Preparations are now well under way. The format of the meeting will be that adopted in previous years with the main meeting running between 27 May and 29 May, with the preceding day (26 May) allocated to the working groups of the society. There are now five active working groups of the society (pacing and electrophysiology, intervention, echocardiography, nuclear medicine, and paediatrics). Each group produces its own programme for the Tuesday afternoon which members of the Society may wish to attend. It has been suggested that the programmes of the working groups might be more closely integrated with the main meeting in future years: the newly formed Programme Committee are looking at this option. If you have any views we would like to hear from you. As before there are three plenary sessions in the main programme. The plenary session on 27 May is on epidemiology, chaired by David Wood. The plenary session on 28 May is an update on transplantation, chaired by John Dark. The plenary session on 29 May is an update on thrombolytic and angioplasty trials co-chaired by David de Bono and Anthony Rickards. In each of these sessions there will be presentations from American and continental European speakers. We have been impressed by the number and quality of abstracts submitted this year for the scientific meeting and numbers again have topped previous records. The total of 685 submissions represents a 15% increase on last year: of these a total of 270 (39%) have been accepted for presentation. We have increased the number of posters presented this year, with two separate poster sessions on the Wednesday. The main lectures this year are the Thomas Lewis Lecture to be given by Professor Eugene Braunwald from Harvard and the St Cyres Lecture to be given by Raphael Balcon. As a follow up to the successful meeting held in December we will be discussing the developing internal market in cardiology and cardiac surgery. The other innovation this year is a session primarily aimed at the district general hospital cardiologists. This session is to be chaired by Andrew McLeod. Speakers will discuss some of the controversies in contemporary cardiological practice. We would like to hear your views about this experiment. As can be seen from the changes outlined above, the society is slowly modifying the format of the Annual Scientific Meeting in response to members requests and needs. To facilitate this process we have organised a Programme Committee that is chaired by Andrew Henderson. The committee comprises Ronnie Campbell, Andrew McLeod, Duncan Dymond, and Paul Oldershaw. It met formally for the first time recently to formulate the programme for Harrogate, and will be meeting again during the course of the meeting to make modifications that can be adopted subsequently at Wembley and Torquay. If you wish to make suggestions to this committee please write to Andrew Henderson. Ideally new ideas should be passed on before the Harrogate meeting because changes take a long time to implement. Areas for debate already include the inter-relation between posters and oral presentations, methods by which poster sessions can be improved, and the balance between presentation of original work and update sessions. You will hear more in future newsletters.

Honours

Members of our society featured in the new year honours. Magdi Yacoub will receive a knighthood on 19 May and Michael Webb-Peploe an OBE on 17 March. We apologise for being late in offering our congratulations. We have more good news. John Camm and Tom Evans have both been made Queen's Honorary Physicians (civilian).

Our newsletters have been getting longer, a trend we may not be able to reverse . . . We have decided to try subheadings. We hope this will not encourage colleagues to be selective in their reading: that would be at the peril of missing vital information, and assuredly cannot be recommended.

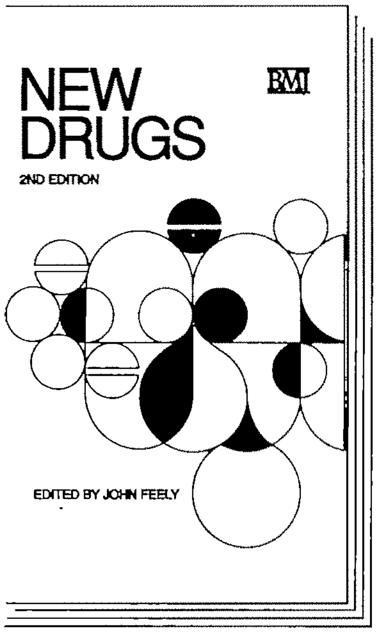
DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
9 Fitzroy Square
London W1P 5AH

NOTICE

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts was 3 January.

What's best for patients?



New drugs are continually being developed and knowledge about existing drugs is constantly expanding, so it is essential, but difficult, for doctors to keep up to date with the latest developments. *New Drugs* describes the most important therapeutic advances of the past decade and discusses the drugs that will be in common use in the 1990s. Completely revised and updated, this second edition has been expanded to include 11 additional chapters. Its coverage of practical aspects of drug use, avoidance of adverse reactions and interactions, and prescribing at extremes of age makes it an invaluable guide for busy practitioners who want to get the best out of the new drugs currently available.

Chapters include: **Adverse reactions to drugs • Calcium antagonists • Diuretic treatment • Antiarrhythmic drugs • Insulin • Lipid lowering drugs • Antidepressant drugs • Centrally acting drugs • Controlling symptoms in advanced cancer**

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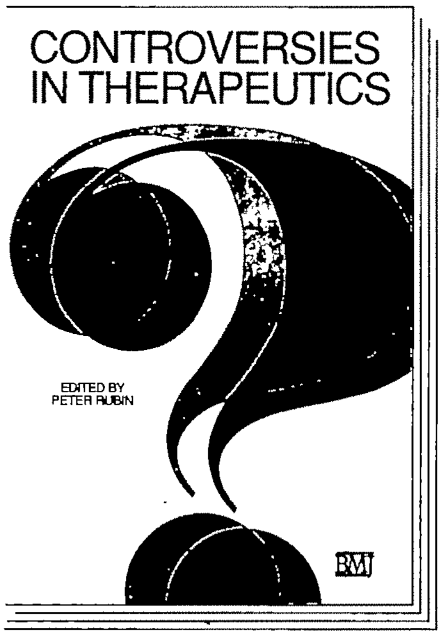

Doctors do not always agree on what is the right treatment even for quite common conditions. Often definitive clinical trials have not been performed and no one knows for sure the best way to treat. *Controversies in Therapeutics* looks at some problems that arise in general practice. For each one it offers two different approaches; and Peter Rubin, professor of therapeutics and consultant physician at the University Hospital of Nottingham, provides an editorial comment on these which summarises the prevailing views and helps you to make up your own mind. Written by academic experts with everyday clinical experience, *Controversies in Therapeutics* is a must for all physicians and general practitioners—both those who think they know it all and those who know they don't.

Chapters include: **Role of diet in treating atopic eczema • Risks of dependence on benzodiazepine drugs • Thrombolysis and the general practitioner • Depression in childhood • Theophylline in the management of airflow obstruction • Management of constipation**

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". . . in the course of a year at least half the journals on the shelves are never looked at at all."
"Most editors . . . are 'half nun, half whore.'"
". . . in the 300 years of their existence journals have done little to examine their own practices."
"What *are* editors?"
"'If an editor does not please himself,' he used to say, 'he will not please anybody.'"
"Defensive editing we do not need."
"Medical journals in developing countries are, with very few exceptions, unattractive."
"I believe that the future for general medical journals—particularly those published in English—is bright. They will undoubtedly change, but they will not disappear."

The debate was lively and the opinions conflicting and forcefully expressed when, to mark its 150 year past, the *BMJ* decided to join with other general medical journals in examining their perhaps not too certain future. At a conference at Leeds Castle editors of major general medical journals throughout the world, with experts in information science, sociology, and epidemiology, discussed the functions and effectiveness of modern journals, and debated possible choices for development. Edited by Stephen Lock, *The Future of Medical Journals* is a unique compilation of papers on this important but little analysed aspect of medical science.

September 1991
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Peer review is one of the key processes at several stages of scientific research, applications for a research grant, assessing an abstract of a contribution submitted to a meeting of a scientific society, and refereeing a paper for publication in a journal. Without publication, which entails such preliminary validation (continued afterwards by the journal's general and specialist readers), science cannot advance. And ensuring that peer review is as accurate, fair, and quick as possible is one of the principal tasks of most scientific editors.

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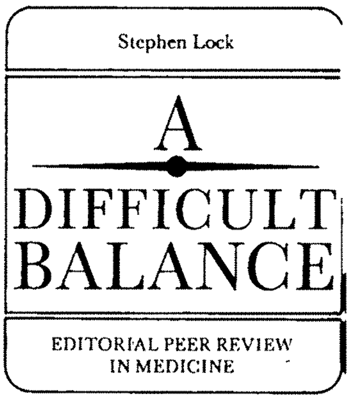

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Essential reading

THE HEALTH OF THE NATION: THE BMJ VIEW

EDITED BY RICHARD SMITH, EDITOR OF THE BMJ

"... a strategy imposed by the government which takes no heed of the views of those who will have to implement it... is valueless".
So writes William Waldegrave, Secretary of State for Health, in his introduction to *The Health of the Nation*, the government's consultative document that sets out a strategy for improving the health of the English. Taking Mr Waldegrave at his word on wanting to listen to everybody, the *BMJ* commissioned a series of articles that explain the views of some of those most concerned. Contributors discuss each of the 16 key areas defined in the strategy and suggest other subjects that might qualify as key areas. One article, from the Radical Statistics Health Group, is strongly critical of the strategy; others are critical of various aspects of it, but almost all of the contributors support the idea of setting targets for improving health. Originally published in the *BMJ*, this collection of articles is an important contribution to the debate on how to achieve health for the nation. Furthermore, the articles will be useful beyond the borders of England because most developed countries are now setting strategies to improve health.

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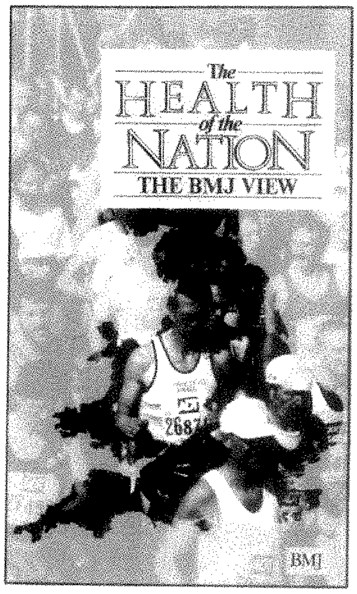

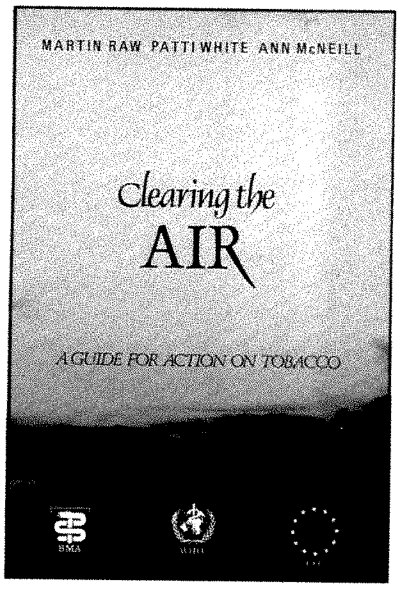
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This practical guide provides an innovative approach to the analysis of tobacco control initiatives, resulting from cooperation between the British Medical Association, World Health Organization, Commission of the European Communities.
It draws on the experience of tobacco control advocates around the world through a set of case studies, each describing a particular action or programme, and highlights the reasons for success. Included are classic campaigns for legislation in Australia and Canada, different approaches to the control of tobacco advertising, and action at community level. Uniquely, each case study finishes by listing key actors involved in the story, who can provide readers with further information. Finally, a substantial resources section listing key organisations and resources worldwide will help readers to take the next steps to action.
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SIDE EFFECTS: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.
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CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

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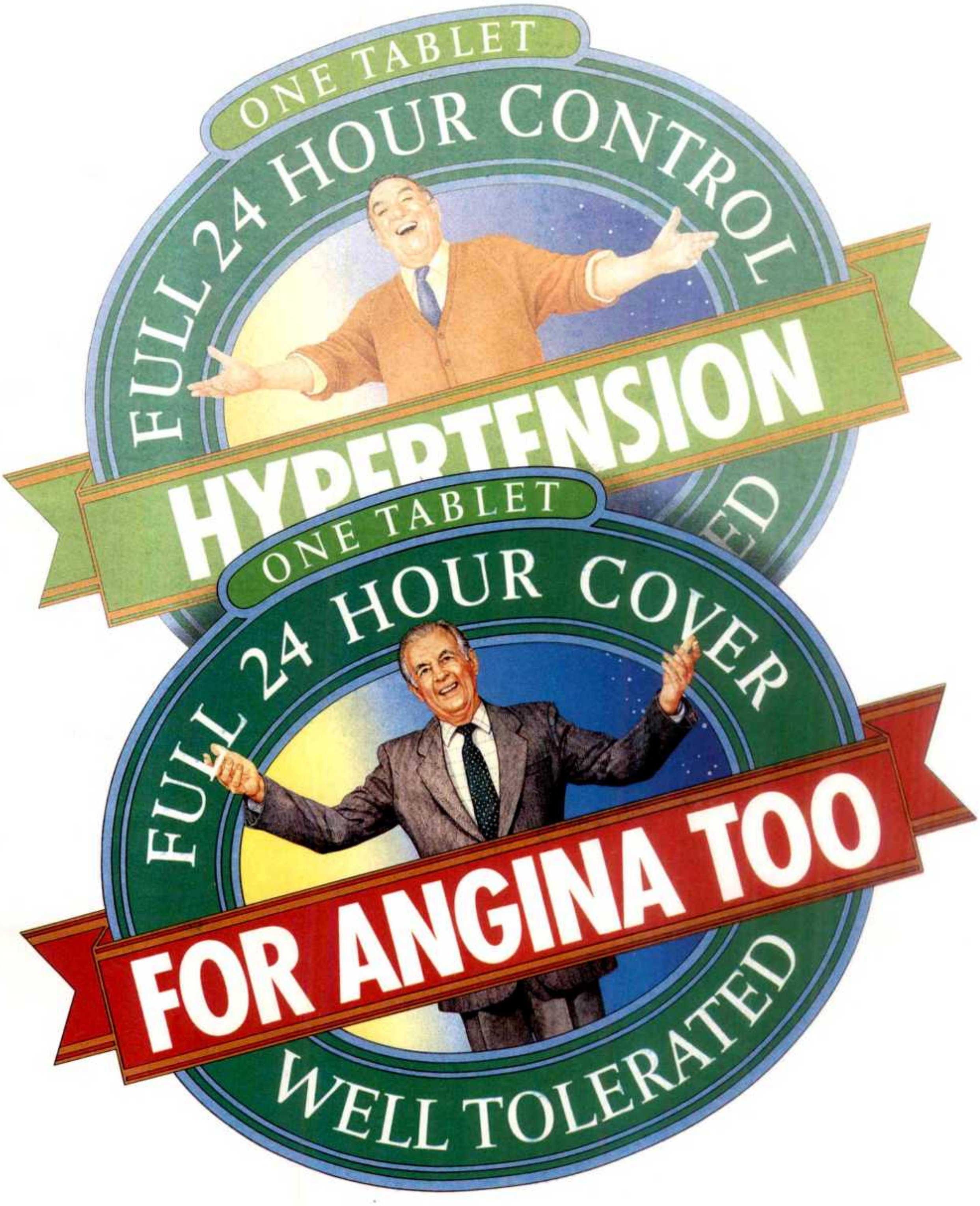

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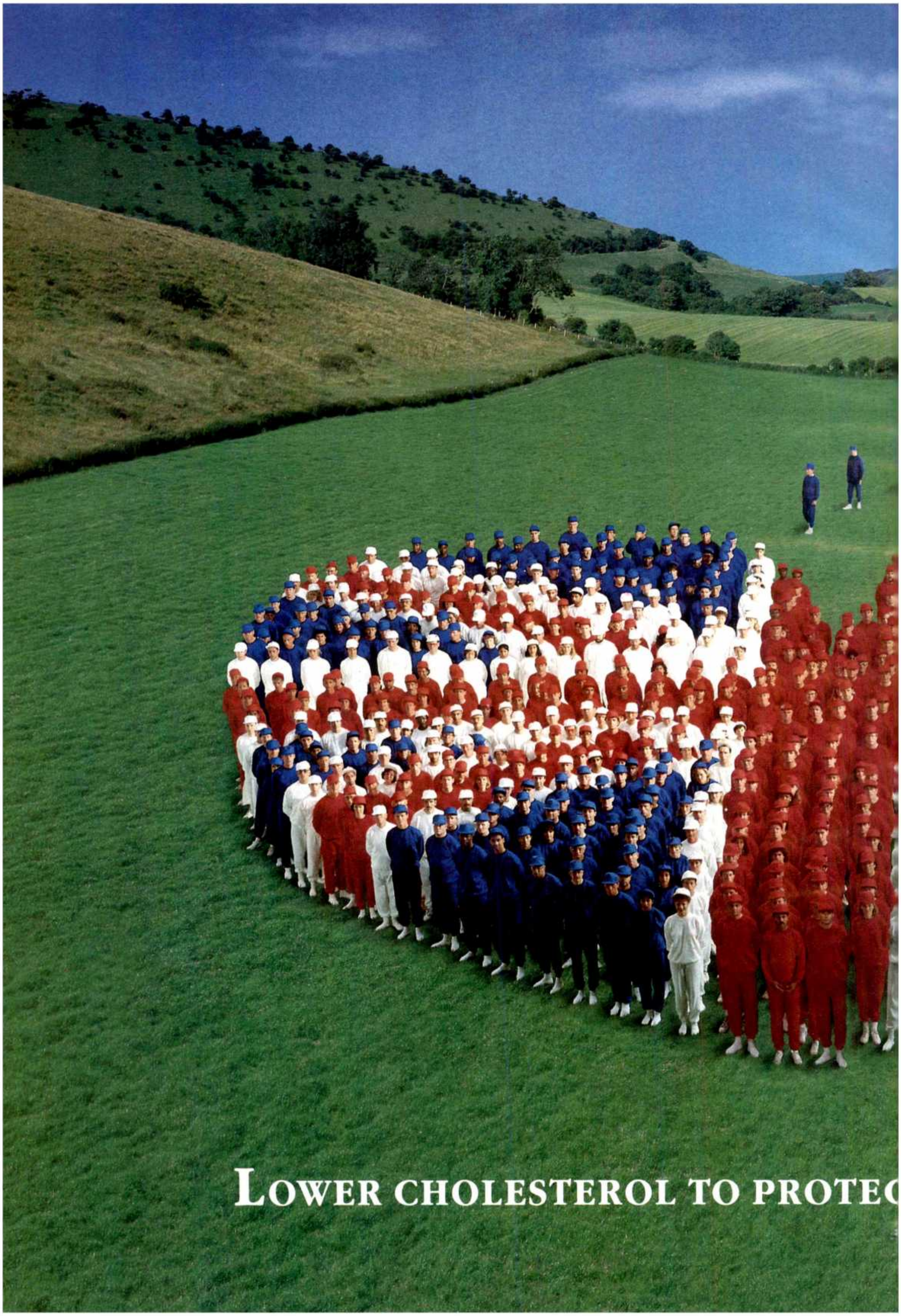
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IE HEART OF THE NATION

- In 1989, coronary heart disease caused 26% of all deaths in England, Wales, and Scotland[1]
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- 'Zocor' is indicated in patients with primary hypercholesterolaemia with a cholesterol level of 6.5 mmol/l or greater and resistant to dietary control.

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ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS Primary hypercholesterolaemia unresponsive to diet with a cholesterol level of 6.5 mmol/litre or greater.

DOSAGE AND ADMINISTRATION Initially 10 mg *nocte*; dose range 10-40 mg once daily *nocte*. Maximum therapeutic response occurs within four to six weeks. Consider dose reduction if total serum cholesterol level falls below 3.6 mmol/l or if LDL cholesterol falls below 1.94 mmol/l. (See Data Sheet for full dosage instructions.) A standard cholesterol-lowering diet should be continued. *Concomitant therapy:* 'Zocor' is effective alone or in combination with bile-acid sequestrants. Lowest recommended dose should be used with immunosuppressants. *Impaired renal function and elderly patients:* Modification of dose should not be necessary. *Children:* Studies to show safety and efficacy have not been done.

CONTRA-INDICATIONS Hypersensitivity to this product; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast-feeding; women of child-bearing potential unless adequately protected by non-hormonal methods.

PRECAUTIONS *Homozygous familial hypercholesterolaemia:* 'Zocor' is unlikely to be effective. *Hypertriglyceridaemia:* 'Zocor' is not indicated where hypertriglyceridaemia is the abnormality of most concern. *Hepatic effects:* Initial and periodic liver function monitoring recommended. Discontinue if persistent enzyme elevations occur, particularly if they rise to three times the upper limit of normal. Caution in patients with a history of liver disease and/or alcoholism. *Muscle effects:* Clinically insignificant transient mild elevations of creatine phosphokinase have been seen. Therapy with 'Zocor' should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected. *Pregnancy:* Contra-indicated. One month should elapse between ending therapy with 'Zocor' and planned conception. *Drug interactions:* Care should be taken in patients on concomitant lipid-lowering therapy, particularly fibrates or nicotinic acid derivatives or immunosuppressive therapies.

SIDE EFFECTS Side effects reported in controlled clinical trials: abdominal pain, constipation, flatulence, asthenia, and headache. Rarely, myopathy. Side effects reported either in long-term extension studies or in marketed use: nausea, diarrhoea, rash, dyspepsia; and rarely, rhabdomyolysis and hepatitis. Isolated cases of angioneurotic oedema also have been reported.

BASIC NHS COST 10 mg tablets, £18.29 for 28-tablet calendar pack. 20 mg tablets, £31.09 for 28-tablet calendar pack.

Product licence numbers: 10 mg tablets, 0025/0241.
20 mg tablets, 0025/0242. Issued December 1991.

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REFERENCES
1. OPCS Monitor DH2, June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

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ABRIDGED PRESCRIBING INFORMATION (Refer to full data sheet before prescribing) **Presentation:** Pink lacquered tablets each containing 30mg or 60mg nifedipine in a controlled release formulation, one side marked Adalat 30 or Adalat 60. **Indications:** Mild to moderate hypertension. **Dosage and Administration:** Adalat LA tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up. One 30mg tablet once daily swallowed whole with a glass of fluid to be taken at approximately 24 hour intervals, preferably during the morning. Dosage can be increased according to individual requirements up to a maximum of 90mg once daily. Patients controlled on Adalat capsules or Adalat Retard may be safely switched to Adalat LA at the recommended initial dose of 30mg once daily, with subsequent titration to a higher dose as clinically warranted. *Renal impairment* Dosage adjustment should not be necessary. *Elderly* Dosage adjustment not usually necessary. *Children* No recommendations for use. **Contra-indications, warnings etc. Contra-indications:** Known hypersensitivity to nifedipine; women of child-bearing potential and nursing mothers; hepatic impairment; history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract; inflammatory bowel disease. **Warnings and precautions:** If used in combination with beta-blocking drugs and other antihypertensives, a possible additive effect resulting in postural hypotension should be borne in mind. Adalat LA will not prevent possible rebound effects after cessation of other antihypertensive therapy. Caution in patients whose cardiac reserve is poor. If ischaemic pain is observed following the introduction of therapy, discontinue treatment. Diabetic patients may require adjustment of their control. **Interactions:** Interactions have been observed with cimetidine and quinidine. **Side-effects:** Headache, dizziness, flushing and gravitational oedema. Less common side-effects include rash, nausea, lethargy and increased frequency of micturition, hypersensitivity-type jaundice, and gingival hyperplasia which may regress on withdrawal of therapy. **Legal category:** POM **Package Quantities and Basic NHS Cost:** Calendar packs containing 28 tablets; Adalat LA 30 £11.76, Adalat LA 60 £15.40. **Product Licence Numbers :** PL 0010/0174-0175 **Date of Preparation:** April 1992.

References: 1. Chung M *et al. Hosp Formul* 1990; **25** (Suppl A): 15-19. **2.** Cruickshank J M & McCainsh J. *Acta Therapeutica* 1992; **18:** 53-59. **3.** Data on file.

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Br Heart J 1992;67:341–2

BRITISH
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Editorial

Coronary heart disease in Indians, Pakistanis, and Bangladeshis: aetiology and possibilities for prevention

High rates of coronary heart disease in people of South Asian (Indian, Pakistani, and Bangladeshi) origin were first reported from Singapore, South Africa, and Trinidad in the 1950s;[1] similar findings were recorded in the United Kingdom at the time of the 1971 census.[2,3] Reliable population-based data on coronary mortality from South Asia are not available but in two northern Indian cities the prevalence of electrocardiographic major Q waves was reported to be at least as high as in European populations.[4,5] In England and Wales in 1979–83 coronary mortality was 36% higher in men born in South Asia and 46% higher in women born in South Asia aged 20–69 years than in the general population.[6] This narrowing of the sex difference in coronary risk occurs in other overseas South Asian populations; in South Africa in 1985 the relative risk of coronary death in Indians compared with Europeans was 1·3 in men and 1·7 in women.[7] The relative risk of coronary disease in South Asian men is highest at early ages: in 1979–83 coronary mortality in men aged less than 40 years born in South Asia was more than twice the national average.[6] The high coronary mortality is common to Gujarati Hindus, Punjabi Sikhs, and Muslims from Pakistan and Bangladesh.[8,9] The consistency of the high risk of coronary heart disease in urban South Asian populations around the world, affecting both sexes and with early onset, suggests a common underlying explanation.

The clinical picture in South Asian patients with coronary heart disease is similar to that in Europeans. Smoking in South Asian patients is generally less common, average plasma cholesterol concentrations are lower and diabetes is more common than in European patients.[10,11] In patients referred for angiography the anatomical distribution of disease does not differ between South Asians and Europeans although the extent and severity of lesions are greater in South Asians.[10,12] In population surveys differences between South Asians and Europeans in smoking, blood pressure, serum cholesterol, or haemostatic activity do not explain the high risk in South Asians.[13–15] Smoking rates are higher in Bangladeshi men[15] and average blood pressures are higher in Sikhs[16] than in the native British population but in other groups from South Asia the levels of these risk factors are similar to or lower than the average for the general population. Plasma cholesterol concentrations are similar to or lower than the national average in all main groups of South Asian origin.[14–16] Atherogenic constituents in ghee (clarified butter) used in north Indian cooking have been suggested as a possible cause of high coronary risk in South Asians[17] but this fails to explain the high risk in people originating from southern India[8] where ghee is less commonly used.

Non-insulin dependent diabetes is present in about 20% of South Asian men and women aged over 40 years in the United Kingdom, compared with about 5% of Europeans.[16] Similar prevalence rates have been reported for other overseas South Asian populations[1] and for an urban population in southern India.[18] Most South Asian patients with coronary disease are not diabetic[11] and glucose intolerance cannot alone explain more than a small proportion of the excess coronary risk in South Asian people.[19] It is now clear that the high prevalence of diabetes in South Asians is but one manifestation of a pattern of physiological disturbances related to insulin resistance in this group:[15,16] these disturbances include hyperinsulinaemia, hypertriglyceridaemia, low concentrations of plasma high density lipoprotein cholesterol, and hypertension. The mechanisms underlying these associations are poorly understood. Resistance to insulin-stimulated glucose uptake is probably responsible for the glucose intolerance, hyperinsulinaemia, and hypertension. Failure of insulin to suppress release of non-esterified fatty acids from adipose tissue may cause hypertriglyceridaemia,[20] low plasma concentrations of high density lipoprotein cholesterol, and changes in the composition and size of particles in the low density lipoprotein fraction.[21] Insulin resistance is associated with a pattern of obesity in which a high proportion of body fat is deposited intra-abdominally; this central obesity tends to develop in South Asians although the average body mass index is no higher in South Asian men than in European men.[16] The ability to store fat in intra-abdominal depots and rely on non-esterified fatty acids rather than glucose as fuel for muscle may have been selected as a thrifty genotype[22] in a time of scarcity.

The insulin resistance hypothesis provides a unifying explanation for the high rates of both non-insulin-dependent diabetes and coronary disease in South Asians. The lessening of the sex difference in coronary risk in this group is also explicable because insulin resistance is associated with several risk factors that are normally less prevalent in women than in men: these include central obesity, raised concentrations of plasma triglyceride, and lower concentrations of plasma high density lipoprotein cholesterol. A similar loss of female protection against coronary heart disease occurs in non-insulin-dependent diabetes.[23] If the high risk of coronary artery disease common to all groups originating from South Asia results from insulin resistance, this effect cannot be mediated mainly through blood pressure or high density lipoprotein cholesterol: blood pressures are not high in Muslims or Gujarati Hindus, and the concentration of high density lipoprotein cholesterol is no lower in Sikhs than in native British men.[16]

A reduction in the risk of coronary heart disease in South Asians is likely to require different strategies from those recommended for the general population. Control of smoking may help to reduce coronary risk in Hindu and Muslim men, whose smoking rates are similar to the national average, but not in South Asian women or Sikh men who rarely smoke.[16] The basis for advising South Asian communities to reduce saturated fat intake on a mass scale so as to lower average plasma cholesterol is open to question. In Gujarati Hindus saturated fat intake and plasma cholesterol are considerably lower than the national average,[13 14 16] yet mortality from coronary disease in this group is at least as high as in other groups from South Asia whose saturated fat intake and plasma cholesterol are close to the national average.[8 9] Control of obesity and increased physical activity are likely to be the most effective means of reducing the risk of coronary disease in South Asians if the insulin resistance hypothesis is correct. Criteria for ideal weight based on data for Europeans may be inappropriate for South Asians because of differences in body frame size and fat distribution. The efficacy of weight loss and physical training in reversing insulin resistance in South Asians has yet to be demonstrated. Prevention of diabetes and coronary disease may require control of obesity and regular exercise to be maintained throughout life in South Asians.

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1 McKeigue PM, Miller GJ, Marmot MG. Coronary heart disease in South Asians overseas—a review. *J Clin Epidemiol* 1989;42:597–609.
2 Tunstall Pedoe H, Clayton D, Morris JN, Brigden W, McDonald L. Coronary heart attacks in East London. *Lancet* 1975;ii:833–8.
3 Marmot MG, Adelstein AM, Bulusu L. Lessons from the study of immigrant mortality. *Lancet* 1984;i:1455–58.
4 Sarvotham SG, Berry JN. Prevalence of coronary heart disease in an urban population in northern India. *Circulation* 1968;37:939–53.
5 Chadha SL, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N. Epidemiological study of coronary heart disease in urban population of Delhi. *Indian J Med Res* 1990;92:424–30.
6 Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. *Br Med J* 1991;302:560–4.
7 Steinberg WJ, Balfe DL, Kustner HG. Decline in the ischaemic heart disease mortality rates of South Africans, 1968–1985. *S Afr Med J* 1988;74:547–50.
8 Balarajan R, Adelstein AM, Bulusu L, Shukla V. Patterns of mortality among migrants to England and Wales from the Indian subcontinent. *Br Med J* 1984;289:1185–7.
9 McKeigue PM, Marmot MG. Mortality from coronary heart disease in Asian communities in London. *Br Med J* 1988;297:903.
10 Lowry PJ, Glover DR, Mace PJ, Littler WA. Coronary artery disease in Asians in Birmingham. *Br Heart J* 1984;52:610–13.
11 Hughes LO, Cruickshank JK, Wright J, Raftery EB. Disturbances of insulin in British Asian and white men surviving myocardial infarction. *Br Med J* 1989;299:537–41.
12 Hughes LO, Raval U, Raftery EB. First myocardial infarctions in Asian and white men. *Br Med J* 1989;298:1345–50.
13 McKeigue PM, Marmot MG, Adelstein AM, *et al.* Diet and risk factors for coronary heart disease in Asians in north-west London. *Lancet* 1985;ii:1086–90.
14 Miller GJ, Kotecha S, Wilkinson WH, *et al.* Dietary and other characteristics relevant for coronary heart disease in men of Indian, West Indian and European descent in London. *Atherosclerosis* 1988;70:63–72.
15 McKeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE, Rahman S, Riemersma RA. Diabetes, hyperinsulinaemia and coronary risk factors in Bangladeshis in east London. *Br Heart J* 1988;60:390–6.
16 McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;337:382–6.
17 Jacobson MS. Cholesterol oxides in Indian ghee: possible cause of unexplained high risk of atherosclerosis in Indian immigrant populations. *Lancet* 1987;ii:656–8.
18 Ramachandran A, Jali MV, Mohan V, Snehalatha C, Visnawathan M. High prevalence of diabetes in an urban population in south India. *Br Med J* 1988;297:587–90.
19 Miller GJ, Beckles GLA, Maude GH, *et al.* Ethnicity and other characteristics predictive of coronary heart disease in a developing country—principal results of the St James survey, Trinidad. *Int J Epidemiol* 1989;18:808–17.
20 Yki-Jarvinen H, Taskinen M-R. Interrelationships among insulin's antilipolytic and glucoregulatory effects and plasma triglycerides in nondiabetic and diabetic patients with endogenous hypertriglyceridemia. *Diabetes* 1988;37:1271–78.
21 Peeples LH, Carpenter JW, Israel RG, Barakat HA. Alterations in low-density lipoproteins in subjects with abdominal adiposity. *Metabolism* 1989;38:1029–36.
22 Neel JV. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'. *Am J Hum Genet* 1962;14:353–62.
23 Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991;265:627–31.

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ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS

All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).

DOSAGE AND ADMINISTRATION

Hypertension: Initially, 5 mg once daily, reduce starting dose to 2.5 mg if over 65 years, on diuretics or renally impaired. Adjust dose according to response; maintenance usually 10-20 mg once daily. Maximum dose 40 mg daily.

Diuretic-treated patients – if possible stop diuretic two to three days before starting 'Innovace'. Resume diuretic later if required.

Congestive heart failure (adjunctive therapy): Initially, 2.5 mg daily in hospital under medical supervision, increasing to the usual maintenance dose of 10-20 mg once daily according to response.

Impaired renal function: May require a lower maintenance dose. 'Innovace' is dialysable.

CONTRA-INDICATIONS

Pregnancy – stop therapy if suspected. Hypersensitivity to 'Innovace'. Patients reacting with angioneurotic oedema to previous ACE-inhibitor treatment.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during therapy where appropriate.

Renal insufficiency; possibility of hypotension especially in ischaemic heart disease or cerebrovascular disease or in volume-depleted patients; surgery/anaesthesia.

Combination with antihypertensives may increase hypotensive effect. In some patients with bilateral renal artery stenosis increased blood urea and creatinine has been seen, especially in patients treated with diuretics and/or those with renal insufficiency. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended.

Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.

SIDE EFFECTS

Side effects include: dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, cough.

Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia, hyponatraemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

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2.5 mg tablets, 0025/0220; 5 mg tablets, 0025/0194; 10 mg tablets, 0025/0195; 20 mg tablets, 0025/0196.

Issued August 1991.

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References

1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

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SQUIB

Br Heart J 1992;67:343–50

Insulin resistance, diabetes, and risk markers for ischaemic heart disease in Asian men and non-Asian men in Bradford

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Accepted for publication 5 February 1992

Abstract

***Objective*—To examine the hypothesis, in a community not studied before, that insulin resistance associated with centralised adiposity is the mechanism underlying the predisposition of Asian immigrant communities to both ischaemic heart disease and diabetes mellitus.**

***Design*—Cross sectional study within one socioeconomic stratum.**

***Setting*—Two factories in the textile sector in Bradford, West Yorkshire.**

***Subjects*—Male manual workers of Asian (110) and non-Asian origin (156) aged 20–65 years.**

***Results*—Diabetes was almost three times more prevalent in the Asian group. Two hours after an oral glucose load Asian men had double the serum insulin concentrations of non-Asian men ($p < 0\cdot0001$). Asian men also had significantly lower concentrations of plasma total cholesterol ($p < 0\cdot03$), high density lipoprotein cholesterol (HDL) (HDL_2, $p < 0\cdot0001$; HDL_3, $p < 0\cdot0001$), and apolipoprotein AI ($p < 0\cdot0001$). Fasting plasma triglyceride concentrations were slightly higher ($p = 0\cdot072$) in the Asian men; thus the ratio of triglyceride cholesterol was higher ($p = 0\cdot006$). The interrelation between serum insulin and plasma lipid concentrations indicated metabolic differences between the ethnic groups. Insulin concentrations were associated with cholesterol concentrations in the Asian men only and there was a lack of association between triglyceride, low density lipoprotein cholesterol, and HDL cholesterol in this group. The risk marker profile in the Asian men was therefore quite different to that of their non-Asian counterparts and was associated with a greater tendency to centralised adiposity.**

***Conclusion*—These data support the insulin resistance hypothesis and thus have important implications for strategies for the prevention of heart disease in Asian communities in the United Kingdom.**

Asian people living in the United Kingdom have a recognised excess of ischaemic heart disease.[1] In an extensive review, McKeigue *et al* concluded that high rates of heart disease are common in other groups of Asians originating from the Indian subcontinent and living overseas.[2] They suggested that the excess rates seen in immigrant Asian communities cannot be explained in terms of the established risk factors for heart disease—that is, raised plasma total cholesterol and high rates of hypertension and smoking. However, studies of such Asian communities by McKeigue *et al* and other groups indicated that probable risk factors in this group are a higher prevalence of non-insulin-dependent diabetes mellitus, lower plasma high density lipoprotein cholesterol concentrations, and higher triglyceride concentrations.[3–7]

McKeigue *et al* hypothesised that insulin resistance may be common in these people and that this may be the underlying mechanism leading to both the predisposition to diabetes and the atherogenic lipid profile observed.[2] A similar combination of risk markers was described by Reaven[8] as "syndrome X", namely, resistance to insulin stimulated glucose uptake, glucose intolerance, hyperinsulinaemia, increased very low density lipoprotein cholesterol, decreased high density lipoprotein cholesterol, and hypertension.

Diabetes, insulin resistance, and cardiovascular disease have separately been associated with a tendency to centralised adiposity, where adipose tissue is deposited preferentially on the trunk and intra-abdominally.[9] Body fat distribution may therefore have a role in the insulin resistance hypothesis of McKeigue *et al* and in Reaven's "syndrome X".

In their latest study McKeigue *et al* tested their hypothesis in a large population survey in London (using factory workers and general practice patients).[10] The results confirmed the existence of the syndrome in the Asian subjects and this was associated with a greater tendency to centralised adiposity. The population studied was predominantly Sikh (52%) with 20% of Hindu and 15% of Muslim culture. Bradford, West Yorkshire, has a high proportion of residents originating from the Indian subcontinent. In the 1981 census, 15% of residents were living in households headed by an Asian-born man.[11] Around two thirds of these were Muslims from Pakistan. It was therefore of interest to investigate the insulin resistance hypothesis in this different Asian community.

This paper describes a study in which a wide range of risk markers, both established ones and ones that were relevant to the hypothesis in question, were measured in Asian and non-Asian men resident in Bradford in 1989. Apolipoproteins AI and B were measured because they are the major protein components of the lipoproteins of interest and they have been suggested as predictors of coronary heart disease risk.[12]

Patients and methods

The protocol for this study was approved by the district ethics committee and informed consent was obtained from all the men.

SUBJECTS

We studied male, skilled manual workers of Asian and non-Asian origin, aged 20–65 years. They were classified as Asian or non-Asian by name and self-reported origin.

SAMPLING

Local firms in the traditional textile industry in Bradford were invited to participate in the study. Two factories that responded were selected on the basis of the number of Asian men in the workforce and the comparability of labour both between and within factories. The study was confined to departments where men of both Asian and non-Asian origins worked together. Because participation in the study was voluntary we made every effort to maximise response rates.

PROCEDURE

The men were asked to complete a lifestyle questionnaire (to obtain demographic details; medical histories; and information on smoking habits, exercise routine, and alcohol use), a food frequency questionnaire, and a three day diet diary. Blood samples were taken during a morning appointment and during an afternoon session; blood pressure was measured, anthropometrical measurements made, and completed questionnaires and diet diaries were checked through with each man. At all times one of the research team (PS) was available to translate into Asian languages.

BLOOD SAMPLES

The men were asked to fast overnight. Venous blood samples were taken between 7 and 8 am, after a minimum of 15 minutes of seated rest, for plasma lipid determinations. Samples for plasma glucose and serum insulin analyses were then taken two hours after ingestion of an oral dose of 75 g glucose (taken in 330 ml Lucozade). The men fasted over the two hour period.

BLOOD PRESSURE

These measurements were made with an electronic sphygmomanometer (Copal, Pulse, UK) by one observer only. Two measurements were made while each man was seated. The first was taken after at least 15 minutes' rest to familiarise the subject with the procedure and the second was taken after a further 15 minutes' rest. Only the second readings were used for the present analyses. A systolic pressure of $\geqslant$160 mm Hg or a diastolic pressure of $\geqslant$90 mm Hg or both were the criteria for raised blood pressure.

LIFESTYLE ASSESSMENT

Smoking habit was recorded as never, ex, or current; for current smokers the usual number of cigarettes smoked per day was also recorded. Usual consumption of alcoholic beverages was recorded as number of glasses of appropriate size and converted to standard units. The men were asked to list physical activity taken during leisure time on a regular basis—that is, every week for at least 20 minutes each time. These activities were coded as light, moderate, or strenuous according to lists published by the Health Education Authority.[13]

LABORATORY DETERMINATIONS

Lipid/lipoprotein assays were performed in the Clinical Biochemsitry Department, Harrogate General Hospital. Total plasma cholesterol was measured enzymatically by the method of Allain *et al*,[14] modified for the IL Monarch Centrifugal Analyser. Kits were supplied by Instrumentation Laboratory (UK). Calibration was against a secondary standard supplied by Coulter Electronics. Within batch precision was 1·43% at a concentration of 6·23 mmol/l and between batch precision was 2·03% at a concentration of 6·25 mmol/l. High density lipoprotein cholesterol and its subfractions were measured by the polyethylene glycol precipitation method of Gidez *et al*[15] followed by cholesterol measurement as above. Calibration was against a secondary standard (BCL Precilip, UK). Within batch precision was 1·48% at a concentration of 1·23 mmol/l. Between batch precision was 4·3% at the same concentration. The secondary standards described above were validated against human serum pools provided by the Center for Disease Control, (CDC), Bethesda, USA and NHLI for their lipid standardisation programs. The concentration of low density lipoprotein cholesterol was calculated by the Friedwald equation.[16] Triglycerides were measured on an IL Monarch Centrifugal Analyser by a commercially available kit (Instrumentation Laboratories, UK) based on the method of Bucolo and David.[17] The assay was standardised by calculating triglyceride as the triolein equivalent based on the molar absorption coefficient of NADH. Intra-assay precision was 2·20% at a concentration of 2·65 mmol/l and inter-assay precision was 2·63% at 2·63 mmol/l. Apolipoproteins AI and B were measured by a turbidometric immunoassay.[18] The assays were performed on a Monarch 1000 analyser (Instrumentation Laboratories, UK). Standards were referenced to material provided by CDC. The precision of assays both within and between batch was less than 2·6%.

Plasma glucose and serum insulin concentrations were determined in the Clinical Biochemistry Department, Bradford Royal Infirmary. Plasma glucose was assayed along with routine NHS specimens, by an enzymatic method specific for glucose. Samples were assayed on the same day as collection and thus batch precision data are not available. However, samples were subject to routine quality control procedures. The men were classified as normoglycaemic if their glucose concentration two hours after the oral dose was <7·0 mmol/l. Impaired glucose tolerance was suspected when concentrations were between 7·0 and 11·0 mmol/l and diabetes was suspected when concentrations were ≥11·0 mmol/l.[19]

Serum insulin concentrations were measured by a commercially available kit by Radioimmuno assay (Pharmacia, UK). Within assay precision was below 10% over the range of concentrations measured. Control sera were supplied with kits for internal quality control. We also used an external quality control system administered by the Department of Biochemistry, Guildford Hospital. Results from the Bradford laboratory were consistently within the cluster of values reported by participating laboratories and were never classed as outliers.

ANTHROPOMETRY

All anthropometrical measurements were made by one observer only (AW). The men were measured in their underclothes. Weight was measured to the nearest 0·1 kg and height to the nearest 0·1 cm with the head parallel to the floor. The body mass index was calculated as the ratio of weight (kg) to the square of height (m^2). Circumference measurements were made to the nearest 0·1 cm with a tape measure that had a spring balance attached to ensure consistency of measurement pressure. The circumference of the mid-upper arm was measured at the mid-point between the tips of the acromion and the olecranon. The waist was measured as the smallest circumference between the costal margin and the iliac crest. Hip measurements were made at the level of the most lateral point on the great trochanter. Thigh circumference was measured at the position of maximum girth. Skinfold thicknesses were measured with Holtain calipers to the nearest millimetre at five standard sites: triceps, subscapular, suprailiac, anterior thigh, and suprapatellar. Three measurements were taken at each site on the non-dominant side of the body. Data are prestended as arithmetic means.

STATISTICAL ANALYSES

We analysed questionnaire, and clinical data with the *SPSSX Software Program.* Data for plasma triglyceride, high density lipoprotein$_2$ cholesterol, apolipoproteins and serum insulin concentrations were logarithmically transformed, means are therefore geometric. For parametric statistical tests we used two tailed p values unless indicated otherwise. To investigate univariate associations between variables we used Spearman rank correlations (two tailed p values). Multivariate associations were investigated by multiple regression with stepwise addition and deletion of predictor variables. Dietary data will be reported in a separate paper. Because the dietary methods used (food frequency questionnaire and three day diet diary) allow comparison of mean intakes between groups only these data were not entered into the correlation or regression analyses.

*Table 1 Mean (95% CI) plasma glucose, lipids and serum insulin concentrations**

Variable	*Non-Asian (n = 148)*	*Asian (n = 96)*	*p*†
Plasma glucose (mmol/l)	3·5 (3·4 to 3·7)	3·8 (3·7 to 4·0)	0·016
Serum insulin (mU/l)	10·2 (9·1 to 11·5)	22·3 (19·3 to 25·8)	<0·0001
Total cholesterol (mmol/l)	5·7 (5·5 to 5·8)	5·4 (5·2 to 5·6)	0·030
LDL cholesterol (mmol/l)	3·6 (3·5 to 3·8)	3·5 (3·3 to 3·7)	0·283
HDL$_2$ cholesterol (mmol/l)	0·3 (0·3 to 0·3)	0·2 (0·2 to 0·2)	<0·0001
HDL$_3$ cholesterol (mmol/l)	1·1 (1·0 to 1·1)	0·9 (0·8 to 0·9)	<0·0001
Triglyceride (mmol/l)	1·3 (1·2 to 1·4)	1·4 (1·3 to 1·6)	0·072
Triglyceride:cholesterol ratio	0·26 (0·23 to 0·28)	0·32 (0·29 to 0·35)	0·006
Apo AI (mmol/l)	1·2 (1·2 to 1·3)	1·1 (1·1 to 1·2)	<0·0001
Apo B (mmol/l)	0·7 (0·6 to 0·7)	0·7 (0·6 to 0·7)	0·383

*Means for glucose, total, low density lipoprotein (LDL), and high density lipoprotein 3 (HDL$_3$) cholesterol are arithmetic. Means for insulin, HDL$_2$ cholesterol, triglyceride, and apolipoproteins are geometric. All adjusted for age and body mass index (95% CI).

†Significance of F, analysis of variance between ethnic groups (with age and body mass index as covariates).

Results

RESPONSE RATES

Of the eligible men invited to participate, 73·7% from factory A and 76·2% from factory B entered the study. The response rate was higher among Asian men (83·4%) than non-Asian men (70·6%). After entering the study 27 men were lost: four owing to long-term sick leave, three left the factory, nine could not fully meet study requirements because of shift patterns, and 11 withdrew (3·4%). The range of blood analyses was incomplete for 22 men (owing to lack of material). Thus the analyses presented here are based on complete sets of data from 156 non-Asian and 110 Asian men (84·4% of the original sample). In terms of religion, the Asian sample was representative of the Bradford population, with 63·5% Muslims (Pakistani or Punjabi), 31·3% Hindu (mainly Gujarati), and 5·2% either Sikh or of no stated religion. Because of the small sample sizes the results have not been presented for these subgroups.

AGE

The mean age of both ethnic groups was similar (non-Asians 41·0 years, range 20–65 years; Asians 39·3 years, range 20–62 years). Data were adjusted for age where appropriate.

BLOOD PRESSURE

Mean systolic blood pressure was significantly higher in non-Asian men (137·4 mm Hg, 95% CI 134·8 to 139·9) than in Asian men (131·4 mm Hg, 95% CI 128·1 to 134·8) (p = 0·006). Mean diastolic pressure was, however, similar in both groups (non-Asians 79·6 mm Hg (78·0 to 81·2) and Asians 79·5 mm Hg (77·5 to 81·6). However, 26·6% of Asian men in the initial sample were found to have raised blood pressure compared with 23·1% (p = 0·05) of non-Asian men.

DIABETES

By the criteria set out above, seven non-Asian men and 14 Asian men were classified as having suspected diabetes. Of these 21 men, five (23·8%) were undiagnosed upon entry to the study. Diabetes was 2·8 times more common in the Asian men (12·7% *v* 4·5%; difference 8·2%,

Table 2 Inter-correlations between serum insulin, plasma lipids, and waist-to-hip ratio*

	Waist-to-hip ratio	*Serum insulin (mU/l)*	*Cholesterol (mmol/l)*			*Triglyceride (mmol/l)*	*Apolipoprotein AI (mmol/l)*
			HDL 2	*HDL3*	*LDL*		
Insulin (mU/l):							
Non-Asian	0·31§	—	—	—	—	—	—
Asian	0·46§	—	—	—	—	—	—
Cholesterol (mmol/l):							
HDL$_2$							
Non-Asian	−0·24‡	−0·13	—	—	—	—	—
Asian	−0·30§	−0·34§	—	—	—	—	—
HDL$_3$:							
Non-Asian	−0·30§	−0·20†	0·69§	—	—	—	—
Asian	−0·30§	−0·35§	0·64§	—	—	—	—
LDL:							
Non-Asian	0·26‡	0·10	−0·26‡	−0·29§	—	—	—
Asian	0·14	0·21‡	−0·10	−0·07	—	—	—
Triglyceride (mmol/l):							
Non-Asian	0·47§	0·33§	−0·44§	−0·55§	0·28§	—	—
Asian	0·46§	0·31§	−0·46§	−0·47§	0·15	—	—
Apolipoprotein (mmol/l)							
AI:							
Non-Asian	−0·10	−0·15	0·62§	0·74§	−0·10	−0·17†	—
Asian	0·07	−0·04	0·45§	0·67§	−0·01	−0·01	—
B:							
Non-Asian	0·46§	0·28	−0·46§	−0·52§	0·70§	0·80§	−0·24§
Asian	0·40§	0·36§	−0·41§	−0·39§	0·79§	0·80§	0 05

*Spearman rank correlation coefficient (r) with significance (p) (two tailed) <0·05 †, 0·01 ‡, 0·0001 § given for non-Asian men (n = 148) and Asian men (n = 96).

95% CI 1·2 to 15·2 p < 0·02). Only one, a non-Asian man had a two hour glucose concentration within the range for impaired glucose tolerance. For all the other analyses, we used the data for normoglycaemic men only (that is, 148 non-Asian men and 96 Asian men).

SERUM INSULIN, PLASMA GLUCOSE, LIPIDS AND LIPOPROTEINS

Mean glucose concentrations two hours after an oral dose were significantly higher in Asian men (p = 0·016) even though at the same time their serum insulin concentrations were over double those of non-Asian men (p < 0·0001) (table 1). There were significant positive correlations between glucose and insulin concentrations in both Asian (r = 0·514 p < 0·0001) and non-Asian men (r = 0·566 p < 0·0001).

Asian men had significantly lower mean concentrations of total (p = 0·03) and high density lipoprotein cholesterol (p < 0·0001 for both subfractions) and apolipoprotein AI (p < 0·0001). Mean concentrations of low density lipoprotein cholesterol were similar in both ethnic groups. The higher triglyceride concentration in Asian men was of borderline significance (0·05 < p < 0·1). The ratio of triglyceride to cholesterol was significantly higher in Asian men (p = 0·006). Mean concentrations of apolipoprotein B were the same for both groups.

Table 3 Anthropometric measurements (age adjusted arithmetic means (95% confidence interval)

Variable	*Non-Asian (n = 148)*	*Asian (n = 96)*	*p value**
BMI†	25·0 (24·5 to 25·5)	23·8 (23·2 to 24·4)	0·003
MUAC (cm)‡	28·1 (27·6 to 28·5)	27·2 (26·6 to 27·7)	0·008
WHR§	0·90 (0·89 to 0·91)	0·92 (0·91 to 0·94)	0·004
Thigh circumference (cm)	50·4 (49·7 to 51·0)	48·2 (47·4 to 48·9)	<0·0001
Triceps skinfold (mm)	11·9 (11·3 to 12·5)	13·2 (12·4 to 13·9)	0·011
Subscapular skinfold (mm)	16·5 (15·7 to 17·2)	18·9 (18·1 to 19·8)	<0·0001
Suprailiac skinfold (mm)	14·2 (13·3 to 15·2)	17·9 (16·7 to 19·1)	<0·0001
Thigh skinfold (mm)	12·7 (12·1 to 13·4)	13·9 (13·0 to 14·7)	0·032
Suprapatellar skinfold (mm)	8·8 (8·4 to 9·2)	9·1 (8·6 to 9·6)	0·305

*Significance of F, analysis of variance between ethnic groups (age in years as covariate).
†Body mass index: weight/height^2.
‡Mid upper arm circumference (cm).
§Ratio of waist (at least circumference) (cm) to hip circumference (cm).

ASSOCIATIONS BETWEEN SERUM INSULIN AND PLASMA LIPIDS

In both ethnic groups there were significant (p < 0·0001) positive correlations between insulin and triglyceride concentrations (table 2). Insulin was significantly and positively correlated with low density lipoprotein cholesterol and apolipoprotein B in Asian men (p < 0·01 and p < 0·0001) but not in non-Asian men. Similarly, insulin was strongly inversely correlated with high density lipoprotein cholesterol in Asian men (p < 0·0001 for both subfractions) whereas in non-Asian men there was a weak correlation with HDL$_3$ cholesterol only (p < 0·05).

INTRA-LIPID CORRELATIONS

Inter-ethnic differences were seen, in that significant inverse correlations between both high density lipoprotein cholesterol subfractions and low density lipoprotein cholesterol (p < 0·01, p < 0·0001) and between apolipoprotein B and apolipoprotein AI (p < 0·0001) were found only in the non-Asian group. Similarly, the positive correlation between low density lipoprotein cholesterol and triglycerides was only significant in non-Asians (p < 0·0001).

ANTHROPOMETRY

Table 3 shows the anthropometric data. The mean body mass index was significantly lower in the Asian group (p = 0·003). Mid upper arm (upper body) and thigh (lower-body) circumferences were significantly greater in non-Asian men (p = 0·008, p < 0·0001). In contrast, the mean waist-to-hip ratio was higher in Asian men (p = 0·004). Skinfold thicknesses were greater in Asian men at all sites, but the ethnic differences in mean thickness were greatest for

Table 4 Smoking habits, exercise routine, and usual alcohol consumption

Data	*Non-Asian (n = 148)*	*Asian (n = 96)*	*p value**
Smokers	65 (43·9%)	42 (43·8%)	p > 0·05
Cigarettes per day†	15·5 (13·3 to 17 6)	9·6 (6·9 to 12·4)	0·001
Alcohol consumers	138 (93·2%)	35 (36·5%)	<0·0001
Units per week	24·3 (21·0 to 27·7)	19·5 (12·6 to 26·2)	0·203
Strenuous exercise‡	122 (82·4%)	87 (90·6%)	>0·05

*Significance of F, analysis of variance between ethnic groups for group means and significance of difference between two proportions.
†Among smokers only.
‡Number (%) *not* taking regular exercise (at least once a week for at least 20 minutes).

the truncal subscapular and suprailiac sites (both $p < 0\cdot0001$). Triceps and thigh skinfolds were only moderately thicker ($p = 0\cdot011$ and $p = 0\cdot032$) and suprapatellar skinfold thicknesses showed no ethnic variation. Because the waist-to-hip ratio is a reliable measure of centralised adiposity,[20] the following results are presented for this anthrompometric measurement only.

ASSOCIATIONS BETWEEN WAIST-TO-HIP RATIO, SERUM INSULIN, AND PLASMA LIPIDS

Strong ($p < 0\cdot0001$) positive correlations were found between insulin concentrations and waist-to-hip ratio in both ethnic groups (table 2), although the correlation coefficient was higher for the Asian group. Triglyceride and apolipoprotein B concentrations were positively correlated ($p < 0\cdot0001$) with waist-to-hip ratio in both ethnic groups; low density lipoprotein cholesterol was correlated with this ratio in non-Asians only ($p < 0\cdot01$). There were inverse correlations between waist-to-hip ratio and high density lipoprotein cholesterol; the weakest correlation was seen in non-Asians for HDL$_2$ cholesterol ($p < 0\cdot01$, others $p < 0\cdot0001$). No significant correlations between apolipoprotein AI and waist-to-hip ratio were found.

Table 5 Multivariate associations between variables implicated in the insulin resistance syndrome*[2]

	R^2 statistic (cumulative)	
Relation	*Non-Asians (n = 148)*	*Asians (n = 96)*
Insulin related to:		
2 h glucose (mmol/l) (+)	0·316	0·256
Triglyceride (mmol/l) (+)	0·386	—
Waist:hip ratio +)	—	0·421
Apolipoprotein (+)	—	0·454
p value	<0·0001	<0·0001
Total HDL cholesterol related to:		
HDL$_3$ cholesterol (mmol/l) (+)	0·935	0·921
HDL$_2$ cholesterol (mmol/l) (+)	0·993	0·991
p value	<0·0001	<0·0001
HDL$_3$ cholesterol related to:		
Apolipoprotein AI (mmol/l) (+)	0·534	0·443
Triglyceride (mmol/l) (−)	0·714	0·659
HDL$_2$ cholesterol (mmol/l) (+)	0·729	—
p value	<0·0001	<0·0001
Apolipoprotein AI related to:		
HDL cholesterol (mmol/l) (+)	0·553	0·406
Triglyceride (mmol/l) (−)	0·629	—
Strenuous exercise (frequency) (+)	0·639	—
Alcohol intake (units/week) (+)	0·648	—
Apolipoprotein B (mmol/l) (−)	—	0·541
p value	<0·0001	<0·0001
Triglyceride related to:		
Apolipoprotein B (mmol/l) (+)	0·611	0·626
LDL cholesterol (mmol/l) (+)	0·753	0·833
Alcohol intake (units/week) (+)	0·766	—
HDL cholesterol (mmol/l) (−)	0·782	—
Waist:hip ratio (+)	—	0·838
p value	<0·0001	<0·0001
Apolipoprotein B related to:		
Triglyceride (mmol/l) (+)	0·611	0·630
LDL cholesterol (mmol/l (+)	0·864	0·899
p value	<0·0001	<0·0001

*Multiple regression with stepwise addition and deletion of variables. Statistic given is adjusted R^2 (cumulative) for the regression equation after addition of each predictor variable. The p value is the significance of the F value for the complete equation—that is, significance of combined predictor variables. Predictor variables were all previously found to contribute significantly and independently to variance of the dependent variables. The sign in parentheses shows the direction of the relation.
HDL, high density lipoprotein; LDL, low density lipoprotein.

SMOKING, EXERCISE, AND ALCOHOL

Table 4 gives details of these aspects of lifestyle. The proportion of non-Asian mean who were current smokers (43·9%) was similar to the proportion among Asian men (43·8%). However, non-Asian smokers smoked more cigarettes per week on average than Asian smokers ($p = 0\cdot001$). Most (93·2%) of the non-Asian men regularly consumed alcoholic beverages whereas only 36·5% of Asian men did. Among alcohol consumers, non-Asian men drank on average more units weekly than Asian consumers, although the difference was not significant. Most (82·4%) of the non-Asian men and even more Asian subjects (90·6%) did not take strenuous exercise regularly.

MULTIVARIATE ANALYSES

We investigated the associations between the biochemical, anthropometrical, and lifestyle variables by multiple regression analyses (stepwise addition and deletion). Predictor variables were chosen according to biological relevance and the strength of the univariate correlation with each dependent variable and were entered into the equation in order of decreasing strength of this univariate correlation. Table 5 summarises the results of these analyses. Only significant (5% level) independent predictors are shown, along with the cumulative (adjusted) R^2 with the significance (F value) of the contribution of combined predictors after allowance for other terms in the equation.

Two hour glucose concentrations and triglyceride concentrations were significant independent predictors of two hour insulin concentrations in non-Asian men; together they accounted for 38·6% of the total variance. In Asian men two hour glucose, waist-to-hip ratio, and apolipoprotein B concentrations made significant contributions; together they accounted for 45·4% of the total insulin variance.

Total high density lipoprotein cholesterol concentrations were almost completely dependent upon the variance of the HDL$_3$ subfraction in both ethnic groups. In turn, HDL$_3$ cholesterol concentrations were significantly related to apolipoprotein AI and triglyceride concentrations. Together these accounted for 65·9% of total variance in Asian men and 71·4% in non-Asian men. In non-Asian men the HDL$_2$ concentration was also found to be a significant predictor.

Apolipoprotein AI concentrations were related to high density lipoprotein cholesterol and triglyceride concentrations in non-Asian men, whereas in Asian men high density lipoprotein cholesterol and apolipoprotein B concentrations were significant independent predictors. In Asian men 54·1% of total apolipoprotein AI variance was explained by these predictors only. In non-Asian men the inclusion of frequency of strenuous exercise and usual weekly alcohol consumption also made significant improvements to the model, so that a total of 64·8% of the variance was explained.

Triglyceride, apolipoprotein B, and low density lipoprotein cholesterol concentrations were closely inter-related in both ethnic groups. However, in non-Asian men alcohol consumption and high density lipoprotein cholesterol concentration also contributed to triglyceride variance, whereas in Asian men the waist-to-hip ratio was a significant independent predictor.

Discussion

We found clear differences in the frequency of risk markers between Asian and non-Asian men. Asian men showed a pattern of risk markers similar to that described by McKeigue *et al* for other immigrant Asian communities in the United Kingdom[3 10] that was consistent with the "syndrome X" described by Reaven,[8] that is: raised concentrations of serum insulin in response to glucose, poorer glucose tolerance, decreased plasma high density lipoprotein cholesterol, raised plasma triglyceride, and an increased risk of non-insulin-dependent diabetes mellitus. "Syndrome X" also includes hypertension. We found limited evidence of an increased tendency to raised blood pressure in our Asian group. Others found higher blood pressure or a higher prevalence of hypertension among Asian groups;[3 6 10] and mortality from strokes was recently reported to be 53% higher in Asian men[1] than the United Kingdom average.

Reaven postulated that where there is resistance to insulin stimulated glucose uptake, deterioration of glucose tolerance can only be prevented if the β cells are able to maintain increased insulin secretion. If this state of hyperinsulinaemia cannot be maintained then loss of glucose tolerance would result, followed by overt diabetes mellitus. Thus a state of hyperinsulinaemia resulting from insulin resistance would be characteristic of individuals or groups at increased risk of diabetes.[8] In our study, serum insulin concentrations in Asian men two hours after glucose loading were over double those of the non-Asian men and yet tolerance was poorer (although still normal) in Asian men. The prevalence of diabetes in the total sample was nearly three times higher in Asian men. Thus there were clear signs of insulin resistance in our, as yet, healthy and normoglycaemic Asian men, who were at an increased risk of diabetes. Three other published studies have measured these variables in Asian communities in the United Kingdom. All three reported insulin concentrations after glucose loading to be at least twice as high in Asian men as in non-Asian men and diabetes to be two[3] and four[7 10] times more prevalent in the Asian communities.

The association between insulin resistance and an increased risk of atherosclerosis may be mediated through the reduced concentrations of plasma high density lipoprotein cholesterol and raised concentrations of plasma triglyceride associated with increased insulin concentrations. The exact mechanisms at work have not yet been fully elucidated but they may involve both an increase in the synthesis of very low density lipoprotein triglyceride (owing to a lack of suppression of adipocyte triglyceride lipase by insulin) and reduced clearance of very low density lipoprotein from the very low density/intermediate density/low density lipoprotein metabolic pathway (caused by lack of stimulation of lipoprotein lipase in adipose tissue by insulin). The result would be a saturation of the pathway and thus an increase in plasma triglyceride concentrations and in the ratio of plasma triglyceride to cholesterol[21 22] as seen in the Asian men. The lack of association between triglyceride, low density lipoprotein and high density lipoprotein cholesterol, and apolipoproteins AI and B in the Asian men certainly accords with this suggested disturbance in lipoprotein metabolism. Plasma triglyceride and high density lipoprotein cholesterol concentrations were inversely correlated in both groups as was reported elsewhere.[23] Overall the inverse correlation between serum insulin and plasma high density lipoprotein cholesterol concentrations was significant only in Asian men. Likewise, a significant positive association between insulin and both low density lipoprotein cholesterol and apolipoprotein B concentrations was found for Asian men only.

Though inferences made from correlational data such as these are limited, our results seem to support the conclusion that the Asian men were showing signs of a disturbance of lipid and lipoprotein metabolism consistent with an atherogenic lipid profile and that this was associated with insulin insensitivity.

In addition to the associations found between insulin and lipid concentrations, strong associations were also seen between an increased tendency to centralised adiposity (represented by the waist-to-hip ratio) and increasing insulin, triglyceride, and apolipoprotein B concentrations and decreasing high density lipoprotein cholesterol concentrations. Such associations have been reported before.[9] However, our Asian men showed a significantly greater tendency to centralised adiposity—that is, a greater waist-to-hip ratio and greater subscapular and suprailiac skinfold thickness, even though their mean body mass index was lower than that of the non-Asian men. Furthermore, the positive association between waist-to-hip ratio and serum insulin concentrations was strongest in the Asian men.

Multivariate analyses were undertaken to explore further these inter-relations. As may have been predicted, glucose and insulin were associated in both ethnic groups as were high density lipoprotein cholesterol and apolipoprotein AI and triglyceride/low density lipoprotein cholesterol/apolipoprotein B. However, of most interest here were the ethnic differences in associations. The waist-to-hip ratio was a significant independent predictor of variance in insulin and triglyceride concentrations in Asian men only. Alcohol consumption and frequency of strenuous exercise were significant contributors in non-Asian men only. Results from multivariate analyses such as these should of course, not be taken to imply cause and effect; variables included were measured with varying degrees of precision and this can amplify or reduce the strength of associations. However, our results do confirm that central adiposity and the "syndrome X" factors are interrelated in Asians and that the interrelation between insulin and lipid metabolism shows ethnic variation.

Our results are remarkably similar, both qualitatively and quantitatively, to the results from McKeigue *et al's* most recent study.[10] In the London community studied, the Asian subjects had a higher prevalence of diabetes, higher insulin and triglyceride concentrations after glucose loading and lower high density lipoprotein cholesterol concentrations. Mean waist-to-hip ratios and truncal skinfold thickness were higher in the Asian group. The results of our correlational analyses also accord with those reported by McKeigue *et al.*

Because McKeigue *et al* studied more people they were able to analyse their data by religious subgroup. In Muslims and Hindus the results for diabetes prevalence insulin and triglyceride concentrations after glucose loading, and measures of central adiposity were similar. We too found no differences between our smaller groups of Muslims and Hindus for these variables (except for triglyceride concentrations after glucose loading, which we did not measure) and also no difference in mean blood pressure. The insulin resistance hypothesis seems to apply equally to both cultures and McKeigue *et al* concluded that because heart disease mortality is high in Hindus, Sikhs, and Muslims, these findings point to the insulin resistance syndrome as the most plausible explanation for their excess risk. However, McKeigue *et al* found within Asian variation for some variables; that is, smoking rates, blood pressure, plasma total cholesterol, and high density lipoprotein cholesterol. We too found higher smoking rates and lower high density lipoprotein cholesterol concentrations in Muslims; and fasting triglyceride concentrations were also higher in this group. These differences are consistent with our dietary information. This is to be reported separately, but in brief, the Muslim diet was higher in meat and lower in vegetables than the Hindu diet, with a resulting lower ratio of polyunsaturated to saturated fatty acids (0·4 *v* 0·6, $p < 0·01$). Only three (4·9%) Muslims drank alcohol regularly, whereas 27 (90%) of Hindus did, but at a moderate level (mean intake 15·4 units per week). Moderate alcohol consumption has been associated with increased concentrations of high density lipoprotein cholesterol.[24]

One hypothesis suggests that diabetes mellitus is the modern result of a thrifty genotype that is capable of overproduction of insulin as an energy conserving mechanism under conditions of periodical famine and low energy intake.[25] An increased incidence of diabetes would therefore be expected in a people transported from such an environment into urban British life. One recent study has compared British Asian residents in Manchester with Asian residents in India (both groups originating from the north west of India). The prevalence of diabetes mellitus and insulin concentrations two hours after glucose loading were, however, similar in both groups, although both were substantially higher than those measured in a British non-Asian control group (Dr J Dhawan, personal communication). Perhaps a comparison of very carefully selected groups with completely contrasting lifestyles would shed more light on aetiology.

If, as our studies suggest, centralised body fat distribution and insulin resistance do play an important part in the predisposition of immigrant Asian communities to atherosclerosis, then there are important implications for prevention. Although smoking, high plasma total cholesterol, and hypertension when present are still likely to confer an increased risk of heart disease in Asian people, perhaps preventive strategies aimed at Asian communities should also target the reduction of the waist-to-hip ratio. How feasible this would be depends on whether central adiposity is an acquired or genetic trait. As yet this is still a subject of debate.[9] A recent study, however, has shown that habitual aerobic exercise reduced the waist-to-hip ratio and also had a beneficial effect in reducing plasma triglycerides and increasing high density lipoprotein cholesterol (Wood, unpublished). Although we can not be sure that the "strenuous" exercise recorded here was aerobic, the significant and independent association between frequency of strenuous exercise and apolipoprotein AI concentrations (and therefore indirectly with high density lipoprotein cholesterol concentrations) that we found accords with the results above. The fact that this association was not seen in Asians, who showed even less inclinication than the non-Asians, to take such exercise regularly suggests that this is one facet of heart disease prevention that needs considerable emphasis in Asian communities.

In our original sample the prevalence of diabetes was almost three times higher in Asian men than in non-Asian men. Almost one quarter of those men classified as diabetic in this study were undiagnosed at entry. We gained the impression that the level of understanding of diabetes among the Asian men was low and compliance with dietary controls was poor. Thus the early detection and control of diabetes also needs to be given greater emphasis in preventive strategies in Asian communities.

We recognise that selection of subjects from male manual workers employed in only two factories in Bradford and a response rate of less than 100% may limit the relevance of our conclusions to other populations. However, the consistency between our data and those of McKeigue *et al's* London studies suggests that our results are not chance findings arising from selection bias but that they do indeed have a wider application.

CONCLUSIONS

Our data, from a different Asian community in the United Kingdom than previously studied, provide further evidence to support McKeigue *et al's* hypothesis that body fat distribution and insulin resistance are of aetiological importance in diabetes and heart disease in immigrant Asian communities living overseas. Strategies for preventing heart disease in mixed ethnic communities need to be reviewed, with greater emphasis being placed on control of diabetes, central adiposity, and increased physical activity in Asian communities.

We thank Dr P McKeigue for help and advice during the planning of this study, Sister V Simpson-Clegghorn and the other nurses for their skilled help, the departments of Clinical Biochemistry and Haematology (Bradford Royal Infirmary) and Chemical Pathology (Harrogate General Infirmary and Leeds General Infirmary) for excellent technical assistance, Dr Jackie McCluney for her help, Mrs Carol Stainton for statistical advice, and Mrs Janice Joyce for secretarial help.

1 Barlarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. *Br Med J* 1991;302:560–4.
2 McKeigue PM, Miller GJ, Marmot MG. Coronary Heart Disease in South Asians overseas: a review. *J Clin Epidemiol* 1989;42:597–509.
3 McKeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE, Rahman S, Riemersma RA. Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in East London. *Br Heart J* 1988;60:390–6.
4 Rubenstein AH, Seftel HC, Miller K, Bersohn I, Wright AD. Metabolic response to oral glucose in healthy South African White, Indian, and African subjects. *Br Med J* 1969;i:748–51.
5 Miller GJ, Beckles GLA, Alexis SD, Byam NTA, Price SGL. Serum lipoproteins and susceptibility of men of Indian descent to coronary heart disease. *Lancet* 1982;i:200–3.
6 Miller GJ, Kotecha S, Wilkinson WH, *et al*. Dietary and other characteristics relevant to coronary heart disease in men of Indian, West Indian, and European descent in London. *Atherosclerosis* 1988;70:63–72.
7 Hughes LO, Cruickshank JK, Wright J, Raftery EB. Disturbances of insulin in British Asian and white men surviving myocardial infarction. *Br Med J* 1989;299:537–41.
8 Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
9 Stern MP, Haffner SM. Body fat distribution and hyperinsulinaemia as risk factors for diabetes and cardiovascular disease. *Arteriosclerosis* 1986;6:123–130.
10 McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;337:382–6.
11 Kernohan EEM. *The Health of Bradford*, Bradford Health Authority Annual Report, 1988.
12 Kukita H, Hamada M, Hiwada K, Kokubu T. Clinical significance of measurements of serum apolipoprotein A-I, A-II, and B in hypertriglyceridaemic male patients with and without Coronary Artery Disease. *Atherosclerosis* 1985;55:143–9.
13 Health Education Authority. *Beating heart disease*. London: Health Education Authority.
14 Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem* 1974;20:470.
15 Gidez LI, Miller GJ, Burstein M, Scagle S, Elder HA. Separation and quantitation of subclasses of human plasma HDL by a simple precipitation procedure. *J Lipid Res* 1982;23:1206–23.
16 Friedwald WT, Levy RI, Fredrickson DS. Estimation of serum low-density lipoprotein cholesterol without the use of the preparative centrifuge. *Clin Chem* 1972;18:499–502.
17 Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 1973;19:476–82.
18 Rifai N, King ME. Immunoturbidometric assays of apolipoprotein A, AI, AII, and B in serum. *Clin Chem* 1986;32:957–61.
19 Report of a WHO study group. *WHO Tech Rep Ser* 1985;727:11.
20 Ashwell M, Cole TJ, Dixon AK. Obesity: new insight into the anthropometric classification of fat distribution shown by computed tomography. *Br Med J* 1985;290:1692–4.
21 Tobey TA, Greenfield M, Kraemer F, Reaven GM. Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics, and plasma triglyceride levels in normotriglyceridaemic man. *Metabolism* 1981;30:165–71.
22 Garg A, Helderman JH, Koffler M, Ayuso R, Rosenstock J, Rashkin P. Relationship between lipoprotein levels and *in-vivo* insulin action in normal white young men. *Metabolism* 1988;37:982–7.
23 Davis CE, Gordon D, LaRosa J, Wood PDS, Halperin M. Correlations of plasma high density lipoprotein cholesterol levels with other plasma lipid and lipoprotein concentrations. *Circulation* 1980;62(suppl IV):24–30.
24 Heiss G, Johnson NJ, Reiland S, Davis CE, Tyroler HA. The epidemiology of plasma high-density lipoprotein cholesterol levels. The Lipids Research Clinic Program Prevalence Study Summary. *Circulation* 1980;62(suppl IV):116–36.
25 Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 1962;14:353–62.

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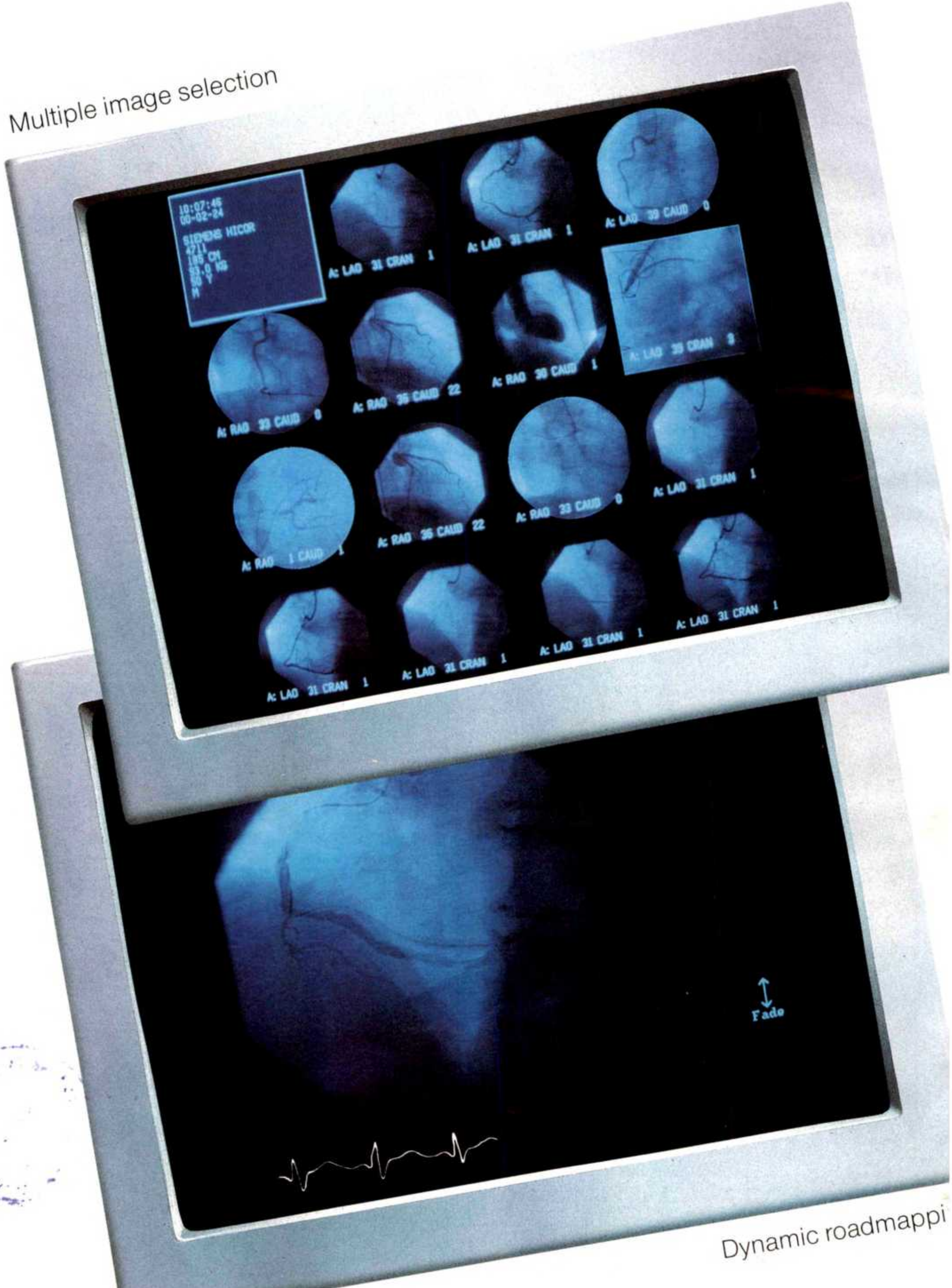

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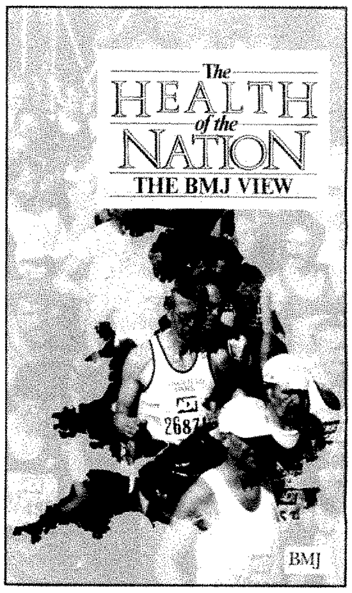

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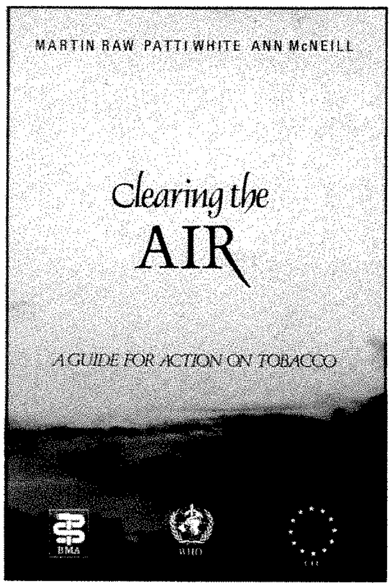
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Strenuous exercise, plasma fibrinogen, and factor VII activity

J B Connelly, J A Cooper, T W Meade

Abstract

***Objective*—To assess the effect of physical activity on plasma fibrinogen and factor VII activity and thus on the risk of ischaemic heart disease.**

***Design*—Cross sectional survey.**

***Setting*—Ten group practices in the Medical Research Council's General Practice Research Framework.**

***Patients*—3967 men aged 45–69 attending screening clinics for the thrombosis prevention trial.**

***Methods*—Structured interview to elicit the intensity and frequency of physical exercise during past month. Measurement of fibrinogen, factor VII activity, cholesterol concentration, blood pressure, and other indices of ischaemic heart disease risk.**

***Results*—Strenuous exercise was associated with significantly lower fibrinogen concentrations than mild exercise, implying a difference of about 15% in the risk of ischaemic heart disease. Strenuous exercise was also associated with lower cholesterol concentrations. More frequent strenuous exercise was associated with lower factor VII activity.**

***Conclusions*—With the recognition of plasma fibrinogen as a strong index of ischaemic heart disease risk the results of this and other studies suggest a pathway through which the protective effect of strenuous exercise may partly be mediated and they provide doctors and patients with a valuable incentive towards prevention, particularly in those whose risk of ischaemic heart disease is substantially due to raised fibrinogen concentrations.**

Plasma fibrinogen concentration is strongly and independently associated with the incidence not only of ischaemic heart disease but also of stroke.[1-3] Whatever the origin of high concentrations—that is, genetic, environmental, or in response to tissue damage—there are several pathways through which they may influence thrombogenesis. These include a contribution to atherogenesis itself, to red cell and plasma viscosity, to platelet aggregability, and to the amount of fibrin deposited.[4-8] Factor VII activity is also associated with the onset of ischaemic heart disease.[1 2] Whether high concentrations of clotting factor are of causal significance can also be studied through the effects of known determinants of ischaemic heart disease on their concentrations, a clear example being that of smoking and fibrinogen.[2 9 10] The protective relation between physical activity at work[11] or in leisure[12] and the incidence of ischaemic heart disease is also well known. Because this exercise has to be current and continuing to confer protection against ischaemic heart disease[12] there is growing reason to believe that vigorous exercise modifies the acute thrombotic component. Pathological findings also suggest that the protective effect of exercise against ischaemic heart disease is mediated through a thrombogenic rather than atherogenic pathway. Thus in the National Necropsy Survey, Morris and Crawford showed that there was no difference in the extent of coronary artery atheroma between those previously in occupations involving light, medium, or heavy physical activity.[13] However, the prevalence of lumen occlusion and, in particular, of large healed infarcts was highest in those whose previous occupations had involved light physical activity, intermediate in those involving medium activity, and lowest in those involving heavy physical activity. The conclusion that exercise exerts its effect on ischaemic heart disease acutely and the practical, preventive implications would be further strengthened by the demonstration that it influences probable thrombogenic mechanisms. We therefore investigated the relation between physical exercise during leisure and plasma fibrinogen concentration and factor VII activity.

Patients and methods

Participants came from ten general practices taking part in an additional study during the screening stage for the thrombosis prevention trial (TPT).[14 15] The purpose of the TPT is to evaluate the effects of low dose aspirin (75 mg) and low intensity oral anticoagulation (International Normalised Ratio (INR) 1·5) in the primary prevention of ischaemic heart disease in high risk men aged between 45 and 69. The first stage consists of a search of practice notes to exclude those who have previously experienced myocardial infarction or a stroke and those in whom antithrombotic threatment is contraindicated (for example, peptic ulceration, requirement for incompatible drugs). Eligible men are then invited for a screening examination, at which the risk of ischaemic heart disease is assessed on the basis of family and smoking history, body mass index (BMI), blood pressure, blood cholesterol, plasma

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Table 1 Relations between personal characteristics and intensity of exercise: numbers (and %) in different categories

	Exercise intensity		
	Strenuous (801 (20·2%))	*Mild (2904 (73·2%))*	*None (262 (6·6%))*
Age group (yr):			
<50	287 (35·8)	595 (20·5)	65 (24·8)
50–60	335 (41·8)	1234 (42·5)	135 (51·5)
>60	179 (22·4)	1075 (37·0)	62 (23·7)
Smoking:			
Never	304 (38·0)	723 (25·0)	58 (22·1)
Ex	175 (21·8)	930 (32·1)	109 (41·6)
Current	322 (40·2)	1238 (42·8)	95 (36·2)
Alcohol:			
Yes	743 (93·1)	2617 (90 2)	228 (87·4)
No	55 (6·9)	283 (9·8)	33 (12·6)
Body mass index:			
<27	520 (64·9)	1783 (61·4)	133 (50·8)
>27	281 (35·1)	1121 (38·6)	129 (49 2)
Occupation:			
Non-manual	473 (60·7)	1277 (45·1)	89 (34·6)
Manual	306 (39·3)	1555 (54·9)	168 (65·4)

Differences between proportions reporting varying intensity by age, smoking habit, and class ($p < 0·0001$); by BMI ($p = 0·0002$); by alcohol consumption ($p = 0·01$).

Numbers approximately same in table 2 (a few missing values for variables other than age, exercise, and fibrinogen).

fibrinogen concentration, and factor VII activity (VII$_c$). The main purpose of the additional study (identification of risk study) was to assess the psychological and behavioural effects of being identified as high risk for a major episode of ischaemic heart disease. During a structured interview the trial nurse also administered questions about exercise. These were similar to those in previously validated methods for distinguishing between active and inactive groups.[16] Mild exercise was defined as a positive response to the question "in the last month have you taken any light activity for the purpose of exercise?" using prompt questions which gave going for a walk, playing golf, or gardening as examples. Strenuous exercise was defined as a positive response to the question "during the past month have you taken part in regular physical exercise that involves a lot of energy output?", with the prompt examples including playing soccer or rugby, jogging, fast swimming, and cycling. Those recording this type of exercise were asked how many times they had undertaken it during the last month. Men were classified as (*a*) those who had taken strenuous exercise (and mild exercise), (*b*) those who had taken mild but not strenuous exercise, and (*c*) those who said they took no exercise.

Current smokers include 400 cigar or pipe smokers whose mean fibrinogen concentration was 2·83 g/l compared with 2·99 g/l in current cigarette smokers. Questions on alcohol consumption divided participants into those who were wholly or virtually teetotal and those who took alcohol occasionally or regularly. Social class is summarised as non-manual (I, II, and III non-manual) or manual (III manual, IV, V) occupation. The body mass index (BMI) is defined as weight/height^2.

χ^2 tests were used to assess the relation between personal characteristics and type of exercise (table 1). Analysis of covariance was used to test the relations between exercise and fibrinogen, VII$_c$, blood pressure, and cholesterol (tables 2, and 3 and 4).

Results

Of the 6187 men invited to the ten screening clinics, 4640 (75%) attended. Of these, 4590 (99%) gave information about lifestyle. A total of 245 men were excluded as ineligible for TPT: 89 because of a definite or possible past history of ischaemic heart disease or other arterial disease (including, for the purposes of this study, angina pectoris and intermittent claudication), 53 because they were on drugs incompatible with TPT treatment, and the rest for other reasons. Of the remaining 4345, 3967 (91%) had complete information on age, exercise, and clotting factors. Table 1 shows that a small proportion (262, 6·6%) did not report even mild exercise. A total of 801 (20·2%) men reported strenuous exercise during the past month (and nearly all these men also reported mild exercise) and the remaining 2904 (73·2%) reported mild exercise only. Compared with the other two groups, those reporting strenuous exercise were younger, were less likely to

Table 2 Mean (SD) fibrinogen concentrations (g/l) according to intensity of exercise

	Exercise intensity			
	Strenuous	*Mild*	*None*	*All*
Age group (yr):				
<50	2·58 (0·55)	2·63 (0·51)	2·61 (0·48)	2·61 (0·52)
50–60	2·63 (0·52)	2·77 (0·57)	2·79 (0·58)	2·74 (0·57)
>60	2·80 (0·58)	2·88 (0·56)	2·99 (0·57)	2·87 (0·57)
Smoking:				
Never	2·55 (0·52)	2·66 (0·52)	2·65 (0·49)	2·63 (0·52)
Ex	2·65 (0·50)	2·73 (0·56)	2·69 (0·55)	2·71 (0·55)
Current	2·83 (0·61)	2·96 (0·55)	2·96 (0·60)	2·94 (0·57)
Alcohol:				
Yes	2·64 (0·54)	2·77 (0·56)	2·77 (0·55)	2·74 (0·55)
No	2·75 (0·58)	2·89 (0·60)	2·93 (0·67)	2·88 (0·60)
Body mass index:				
<27	2·62 (0·55)	2·76 (0·56)	2·76 (0·58)	2·73 (0·56)
>27	2·72 (0·54)	2·81 (0·57)	2·83 (0·55)	2·79 (0·57)
Occupation:				
Non-manual	2·60 (0·53)	2·77 (0·58)	2·69 (0·50)	2·72 (0·54)
Manual	2·71 (0 56)	2·80 (0·55)	2·84 (0·59)	2·79 (0·55)

Within each grouping (age, etc) fibrinogen concentration was lower in those reporting strenuous exercise ($p < 0·0001$).

Effects of age, smoking, alcohol intake, BMI, and occupation on fibrinogen ($p < 0·0001$).

Table 3 Mean values (95% confidence intervals) adjusted for age, smoking, alcohol habit, BMI, and non-manual occupation according to exercise intensity

	Exercise intensity			
	Strenuous (775)	*Mild (2809)*	*None (255)*	*p (F test)*
Fibrinogen (g/l):				
Mean	2·70	2·77	2·70	0·01
95% CI	2·66 to 2·75	2·74 to 2·80	2·70 to 2·82	
VII (% standard):				
Mean	86·5	86·0	88·1	0·35
95% CI	84·6 to 88·4	84·8 to 87·3	85·2 to 91·1	
Systolic blood pressure (mm Hg):				
Mean	135·8	136·0	134·1	0·24
95% CI	134·4 to 137·3	135·0 to 137·0	131·9 to 136·4	
Cholesterol (mmol/l):				
Mean	5·74	5·85	5·87	0·03
95% CI	5·65 to 5·83	5·79 to 5·91	5·74 to 6·01	

BMI, body mass index.

be smokers, drank more alcohol, were less obese, and were more likely to be in non-manual occupations.

Table 2 shows mean fibrinogen concentrations according to type of exercise. Within each of the groupings for the personal characteristics, and without exception, the mean fibrinogen concentration in those reporting strenuous exercise was significantly lower than in those reporting mild or no exercise. Mean values in these last two groups were virtually identical. (Similar tables for systolic blood pressure, cholesterol, and VII_c are available on request and show less consistent or no relations with exercise: see also table 3.)

Table 3 shows mean values (taking account of all the independent variables). The effect of strenuous exercise on fibrinogen remained significant and was probably similar for cholesterol.

Table 4 shows fibrinogen concentration and VII_c according to the number of occasions on which strenuous exercise was reported each month. The trend towards lower values with increasing frequency was statistically significant for VII_c but not for fibrinogen (and there were no suggestive trends for cholesterol or blood pressure).

Discussion

As far as we are aware no large scale study has previously reported in detail on exercise and fibrinogen, in particular. Those that have commented in summary form have all found a trend or a definite effect similar to our results. The clearest result comes from 931 civil servants in the Whitehall study[17] which used a method for eliciting vigorous exercise similar to that of Morris *et al.*[12] The Gothenburg study of 639 men[18] used a subjective four point scale and found an inverse relation between amount of physical activity and fibrinogen, though it was not statistically significant. In a Scottish study of 8824 men and women[19] those inactive in leisure and those who had reduced their level of activity had higher fibrinogen concentrations that those who were and had stayed active—differences that remained after standardising for smoking but not when social class was also taken into account. In a Danish study of 439 men,[20] physical activity was significantly associated with a reduction in fibrinogen when behavioural and social variables were considered separately in multivariate analyses. When the analysis was repeated with simultaneous inclusion of these and several other variables the association was not significant, though measured fitness was associated with a reduction in fibrinogen concentration when all the variables were included. In a Russian study[21] regular physical training in patients with ischaemic heart disease led to a fall in fibrinogen concentrations by comparison with an untrained group.

It is unlikely that the significantly lower fibrinogen concentrations in those reporting strenuous exercise in our study are the result of a selection effect due to health. In particular, those with a definite or possible past history of vascular disease were excluded either at the note-search stage or at screening.

Some misclassification of exercise grouping is likely to have occurred, probably in the direction of over-reporting of strenuous exercise by men who did not in fact exercise to this extent. If so, the true difference in fibrinogen between those taking strenuous exercise, on one hand, and those taking mild or no exercise, on the other, will be larger than our results suggest. We did not enquire about physical activity at work but few occupations now require heavy work and most strenuous physical activity currently takes place during leisure.

The differences in fibrinogen concentration in table 2 between those taking and not taking strenuous exercise are about 0·10 g/l. The relation between fibrinogen concentration and the incidence of ischaemic heart disease is strong. Based on the results of the Northwick Park Heart Study[2] (in which the strength of the association between fibrinogen and ischaemic heart disease is not atypical of the other prospective studies of fibrinogen), a difference of 0·10 g/l would alter the risk of a major event of ischaemic heart disease by about 15%. The smaller difference of about 0·06 g/l in table 3 suggests a change in risk due to strenuous exercise of about 8%, though (as already indicated) both these estimates are probably conservative because of some misclassification of exercise intensity. If it can be assumed that those reporting no exercise took less than those reporting mild exercise, it is noteworthy that in identifying strenuous but not mild exercise as being associated with lower fibrinogen concentrations, our results accord with those of

Table 4 Mean values (95% confidence intervals) adjusted for age, smoking, alcohol habit, BMI, and occupation according to monthly frequency of strenuous exercise

	Frequency/month				
	1–3 (n = 160)	*4–7 (n = 189)*	*8–11 (n = 121)*	*12+ (n = 293)*	*p (F test)*
Fibrinogen (g/l):					
Mean	2·72	2·63	2·68	2·69	
95% CI	2·63 to 2·83	2·54 to 2·74	2·57 to 2·79	2·60 to 2·77	0·63
VII (% standard):					
Mean	87·4	88·6	82·5	82·3	0·003
95% CI	82·8 to 92·3	83·9 to 93·6	77·8 to 87·5	78·5 to 86·2	

Morris *et al*,[12] who found that it was only vigorous exercise that conferred protection against ischaemic heart disease.

The relations of frequency of strenuous exercise with the two clotting factors (table 4) call for further study, to establish or exclude an effect on VII$_c$, in particular, because it is possible[22] that this does respond to very strenuous exercise. There may well have been differential recording inaccuracies of frequency, those claiming to have engaged in strenuous exercise only 1–3 times a month perhaps tending to include a higher proportion who in fact only took mild exercise.

While physical activity probably raises the concentration of high density lipoprotein cholesterol, it has not been consistently associated with a significant reduction in total cholesterol or systolic blood pressure in other population-based samples of adult men.[23 24] Our findings are consistent with this conclusion for blood pressure but suggest an effect of strenuous activity on cholesterol.

The several characteristics that probably influence the risk of ischaemic heart disease through an effect on fibrinogen concentration include[25] advancing age, obesity, diabetes, smoking, use of oral contraceptives and the occurrence of the menopause, low-grade occupation and job "stress", retarded growth during infancy,[26] and (protective) moderate alcohol consumption. Many of these characteristics have similar effects on VII$_c$. We conclude that the protective effect of strenuous exercise can probably be added to this list, further emphasising the central role of coagulability as a mediator of ischaemic heart disease risk.

With the recognition of plasma fibrinogen, in particular, as a strong and independent index of the risk of ischaemic heart disease and the growing availability of fibrinogen measurement, there is increasing interest in aspects of lifestyle that could reduce high concentrations. Dietary changes have little if any effect.[27-29] Stopping smoking is the most effective measure. As table 2 suggests, strenuous exercise may confer an advantage in both smokers and non-smokers. If verified and more precisely quantified in further studies, the apparently beneficial effect of strenuous exercise on fibrinogen could provide both doctors and patients with a valuable and practical incentive towards prevention, particularly where the risk of ischaemic heart disease is substantially due to raised fibrinogen concentrations.

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1 Meade TW, North WRS, Chakrabarti R, Stirling Y, Haines AP, Thompson SG. Haemostatic function and cardiovascular death: early results of a prospective study. *Lancet* 1980;i:1050–4.

2 Meade TW, Mellows S, Brozovic M, *et al.* Haemostatic function and IHD: principal results of the Northwick Park Heart Study. *Lancet* 1986;ii:533–7.

3 Wilhelmsen L, Korsan-Bengtsen K, Welin L, *et al.* Fibrinogen as a risk factor for stroke and myocardial infarction: *N Engl J Med* 1978;311:501–5.

4 Lowe GDO, Blood rheology in arterial disease: *Clin Sci* 1986;71:137–46.

5 Meade TW, Vickers MV, Thompson SG, Stirling Y, Haines AP, Miller GJ. Epidemiological characteristics of platelet aggregability. *Br Med J* 1985;290:428–32.

6 Gurewich V, Lipinski B, Hyde E. The effect of the fibrinogen concentration and the leukocyte count on intravascular fibrin deposition from soluble fibrin monomer complexes. *Thromb Haemost* 1976;36:605–14.

7 Chooi CC, Gallus AS. Acute phase reaction, fibrinogen level and thrombus size. *Thromb Res* 1989;53:493–501.

8 Naski MC, Shafer JA. A kinetic model for the α-thrombin-catalyzed conversion of plasma levels of fibrinogen to fibrin in the presence of antithrombin III. *J Biol Chem* 1991;19:352–6.

9 Meade TW, Imeson JD, Stirling Y. Effects of changes in smoking and other characteristics on clotting factors and the risk of IHD. *Lancet* 1987;ii:986–8.

10 Wilkes HC, Kelleher C, Meade TW. Smoking and plasma fibrinogen (letter). *Lancet* 1988;i:307–8.

11 Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JW. Coronary heart disease and physical activity of work. *Lancet* 1953;ii:1053–7, 1111–20.

12 Morris JN, Clayton DG, Everitt MG, Semmence AM, Burgess EH. Exercise in leisure time: coronary attack and death rates. *Br Heart J* 1990;63:325–34.

13 Morris JN, Crawford MD. Coronary heart disease and physical activity of work. Evidence of a national necropsy survey. *Br Med J* 1958;ii:1485–96.

14 Meade TW, Wilkes HC, Stirling Y, Brennan PJ, Kelleher C, Browne W. Randomized controlled trial of low dose warfarin in the primary prevention of IHD in men at high risk: design and pilot study. *Eur Heart J* 1988;9:836–43.

15 Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. *Am J Cardiol* 1990;65:7c–11c.

16 Washburn RA, Adams LL, Haile GT. Physical activity assessment for epidemiologic research: the utility of two simplified approaches. *Prev Med* 1987;16:636–46.

17 Davey Smith G, Marmot MG, Etherington M, O'Brien JR. A work stress-fibrinogen pathway as a potential mechanism for employment grade differences in coronary heart disease rates [abstract]. Second International Conference on Preventive Cardiology, 1989, Washington DC.

18 Rosengren A, Wilhelmsen L, Welin L, Tsipogianni A, Teger-Nilsson AC, Wedel H. Social influences and cardiovascular risk facts as determinants of plasma fibrinogen concentration in a general population sample of middle aged men. *Br Med J* 1990;300:634–8.

19 Lee AJ, Smith WCS, Lowe GDO, Tunstall-Pedoe H. Plasma fibrinogen and coronary risk factors: The Scottish Heart Health Study. *J Clin Epidemiol* 1990;9:913–9.

20 Moller L, Kristensen TS. Plasma fibrinogen and ischemic heart disease risk factors. *Arteriosclerosis Thrombosis* 1991;11:344–50.

21 Dudaev VA, Dyukov IV, Borodkin VV, *et al.* Change of the level of fibrinogen and its high molecular derivatives as a result of physical training in CHD patients. *Terapevticheskii Archiv* 1986;58:62–6.

22 Gris JC, Schved JF, Feugeas O, Aguilar-Martinez P, Arnaud A, Sanchez N, Sarlat C. Impact of smoking, physical training and weight reduction on FVII, PAI-1 and Hemostatic markers in sedentary men. *Thromb Haemost* 1990;64:516–20.

23 Folsom AR, Caspersen CJ, Taylor HL, Jacobs DR, Luepker RV, Gomez-Marin O. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample: the Minnesota Heart Survey. *Am J Cardiol* 1985;55:21–6.

24 Shaper AG, Wannamethe G. Physical activity and ischaemic heart disease in middle-aged British men. *Br Heart J* 1991;66:384–94.

25 Meade TW. The epidemiology of haemostatic and other variables in coronary artery disease. In: Verstraete M, Vermylen J, Lijnen R, Arnout J. Thrombosis and Haemostasis 1987. Leuven: Leuven University Press, 1987;37–60.

26 Barker DJP, Meade TW, Fall CHD, *et al.* The relationship of fetal and infant growth to plasma fibrinogen in adult life. *Br Med J* 1992;304:148–52.

27 Simpson HCR, Mann JI, Chakrabarti R, *et al.* Effect of high fibre diet on haemostatic variables in diabetes. *Br Med J* 1982;284:1608.

28 Miller GJ, Martin JC, Webster J, *et al.* Association between dietary fat intake and plasma factor VII coagulant activity—a predictor of cardio-vascular mortality. *Atherosclerosis*, 1986;60:269–77.

29 Miller GJ, Cruickshank JK, Ellis LJ, *et al.* Fat consumption and factor VII coagulant activity in middle-aged men. An association between a dietary and thrombogenic coronary risk factor. *Atherosclerosis* 1989;78:19–24.

Br Heart J 1992;67:355–60

Comparative electrophysiological effects of captopril or hydralazine combined with nitrate in patients with left ventricular dysfunction and inducible ventricular tachycardia

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Abstract

***Objective*—To assess the electrophysiological and antiarrhythmic effects of pharmacological load manipulation by an angiotensin converting enzyme (ACE) inhibitor (captopril) and a direct vasodilator (hydralazine plus isosorbide mononitrate) in patients with inducible ventricular tachycardia and impaired left ventricular function.**

***Design*—Randomised open label crossover comparison of three regimens.**

***Setting*—Tertiary arrhythmia referral centre.**

***Subjects*—Eight patients with reduced left ventricular function and sustained ventricular tachycardia inducible by programmed stimulation.**

***Interventions*—Three treatment regimens each of 48 hours duration: captopril, hydralazine plus isosorbide mononitrate, and control (no vasodilator).**

***Main Outcome Measures*—Changes in central haemodynamics, electrophysiological parameters, and induction of ventricular tachycardia during treatment with captopril, or hydralazine combined with nitrate, compared with a control period.**

***Results*—Both vasodilator treatments produced similar balanced reductions in peak systolic pressures and filling pressures compared with controls. Captopril had no effect on sinus cycle length, atrial refractoriness, or intraventricular conduction, but prolonged ventricular effective and functional refractory periods and QT interval during constant rate atrial pacing. Hydralazine combined with nitrate did not significantly alter any electrophysiological variable. Ventricular tachycardia was similarly inducible during all three periods.**

***Conclusions*—Load manipulation by captopril but not hydralazine combined with nitrate prolonged ventricular refractoriness and repolarisation, possibly reflecting a combination of mechano-electrical effect with the restraining influence of ACE inhibitors on reflex sympathetic stimulation.**

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Numerous studies have found an increased risk of sudden death among patients with impaired left ventricular function, thought to be mediated by malignant ventricular tachyarrhythmias in most cases.[1 2] Prevention of these life threatening arrhythmias represents an important goal,[3] but the disappointing results of recent controlled trials including the Cardiac Arrhythmia Suppression Trial (CAST)[4 5] have reinforced concerns about the efficacy and safety of standard antiarrhythmic drugs in the context of reduced ventricular function. By contrast, both angiotensin converting enzyme (ACE) inhibitors and other vasodilator drugs have been shown to improve survival in patients with congestive heart failure.[6 7] With growing awareness of the part played by increased myocardial wall stress and contraction-excitation feedback in the start of arrhythmias associated with left ventricular dysfunction,[8 9] it has been suggested that these benefits of vasodilator therapy might be partly due to protective mechano-electrical effects of load reduction on susceptibility to sudden death. Inhibitors of ACE might also influence propensity to arrhythmia via indirect effects on neuroendocrine activity or sympathetic tone,[10] and direct effects on cardiac myocytes.[11 12] Although there are few data on the electrophysiological properties of these drugs in humans, experimental studies in animals have shown that vasodilators exert antiarrhythmic effects at the ventricular level,[13 14] and this is consistent with clinical reports of reductions in ventricular extra systole on Holter monitoring.[15–17]

The objective of the present study was to evaluate the influence of direct vasodilators and ACE inhibitors on the arrhythmic substrate of the failing heart. Accordingly, we compared the electrophysiological effects of a hydralazine and nitrate combination and captopril, dose titrated to achieve an equivalent degree of load manipulation, in patients with left ventricular dysfunction and ventricular tachycardia induced by programmed electrical stimulation.

Patients and methods

PATIENTS

Patients with impaired left ventricular function and recurrent ventricular tachycardia referred for serial drug testing were included in the study if they fulfilled the following criteria: (*a*) left ventricular ejection fraction <40%; (*b*) sustained (>30 s) monomorphic ventricular tachycardia resembling the spontaneous clinical arrhythmia induced by programmed electrical stimulation; (*c*) not previously established on an ACE inhibitor; (*d*) no amiodarone therapy within the preceding three months. They were excluded if they had had an acute myocardial infarction within the preceding two months or had clinical evidence of decompensated heart failure. Eight consecutive patients (six men, two women) with a mean (SD) age of 67 (6) years were recruited and Table 1 summarises their clinical features. All had coronary artery disease and a history of myocardial infarction with mean (SD) left ventricular ejection fraction of 24 (7)%. The study protocol was approved by the district medical ethics committee and written informed consent was obtained in all cases.

PROTOCOL

As well as routine investigations, all patients underwent left ventricular and coronary angiography and a diagnostic electrophysiological study after withdrawal of antiarrhythmic and vasoactive medication for five half lives. Left ventricular ejection fraction was estimated from the right anterior oblique view using a dedicated software package based on the Dodge formula. Patients meeting the entry criteria proceeded to a randomised open label crossover study comparing electrophysiological and haemodynamic parameters during three treatment periods, each of 48 hours duration. During two limbs of the study, subjects received active treatment with either captopril or hydralazine and isosorbide mononitrate, and during the other, control, limb they received no vasodilator. Oral antiarrhythmic drugs were withheld for the duration of the protocol. Captopril or hydralazine combined with isosorbide mononitrate were administered at eight-hourly intervals (total six doses) with blood pressure monitored every four hours by sphygmomanometry, and dose adjustment aimed at achieving a 10–20% reduction in systolic blood pressure. The starting doses were 25 mg captopril (after a test dose of 6·25 mg), and 50 mg hydralazine combined with 10 mg isosorbide mononitrate, but these were doubled if systolic pressure fell by less than 10% during the first 24 hours or halved if the fall was greater than 20%. All patients underwent combined electrophysiological and haemodynamic assessment at the end of each of the three 48 hour treatment periods.

Table 1 Clinical data

Patient No	*Age/Sex*	*CAD*	*EF (%)*	*LVEDP (mm Hg)*	*TCL (ms)*	*Symptoms*
1	56 / M	2	28	12	240	SCD
2	69 / F	1	15	30	280	Syncope
3	68 / M	2	19	16	330	Presync
4	61 / M	1	30	17	320	Palp
5	70 / M	1	26	16	340	Palp
6	67 / M	1	37	12	350	Syncope
7	73 / M	3	18	32	300	Presync
8	71 / F	1	20	22	270	Presync

CAD, number of diseased coronary arteries; EF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; TCL, cycle length of ventricular tachycardia (presenting episode); Symptoms, symptoms during ventricular tachycardia (presenting episode); SCD, "sudden cardiac death"; Presync, presyncope; Palp, palpitations.

ELECTROPHYSIOLOGICAL AND HAEMODYNAMIC STUDY

Patients were studied after an overnight fast and light premedication with lorazepam between 0900 and 1200 on days 3, 5, and 7 of the protocol—that is, at the end of each 48 hour treatment period. The final dose of vasodilator was given at 0600. All catheters were inserted percutaneously using local anaesthesia with 1% lignocaine and were positioned with fluoroscopic guidance. At the first study on day 3, quadripolar electrodes were introduced via the subclavian approach to the right atrial appendage and right ventricular apex: these electrodes were retained in situ and used for electrophysiological testing at the two subsequent studies on days 5 and 7, avoiding any change in the position of the right ventricular electrode. For haemodynamic assessment, a 7F triple lumen Swan-Ganz catheter was introduced via the femoral vein to the pulmonary artery and an 18G cannula was placed in the femoral artery: these catheters were removed at the end of each study and reintroduced.

After insertion of the catheters and electrodes on each occasion, patients were allowed a 15 minute rest period for stabilisation before any measurements were made. The mean and phasic arterial pressure, pulmonary artery pressure, right atrial pressure, and pulmonary capillary wedge pressure signals were recorded in held expiration with the zero reference at the mid-axillary line. Cardiac output was measured by thermodilution taking the mean of three to five consecutive measurements. The derived indices, calculated from standard equations,[18] were cardiac index, systemic vascular resistance, pulmonary vascular resistance, stroke volume index, and stroke work index. All haemodynamic measurements were duplicated after 10 minutes to ensure stability (<5% variation). The percentage reductions in peak systolic arterial and pulmonary artery pressures compared with the control period were used to assess changes in afterload.

Intracardiac and surface electrocardiographic signals were recorded at a paper speed of 100 mm/s with a multichannel ink jet recorder (Mingograf 7, Siemens-Elema). Pacing and extrastimuli were delivered with a 2 ms pulse width at twice diastolic threshold using a programmable stimulator (Medtronic Model 5328). In addition to sinus cycle length, QRS duration and QT interval (lead V2) were recorded during both sinus rhythm and right atrial pacing at a cycle length of 500 ms. Atrial and ventricular refractory periods were found by the extrastimulus method to the nearest 5 ms at a drive cycle length of 500 ms. After completion of all other electrophysiological and haemodynamic measurements, programmed ventricular stimulation was performed according to a strict 12 stage protocol at the single right ventricular site: single and double extrastimuli were successively introduced during sinus rhythm and drive trains at 600, 500, and 400 ms cycle lengths (stages 1 to 8), scanning diastole with 10 ms increments; triple extrastimuli were then delivered during sinus rhythm and the same three drive cycles (stages

9 to 12). Stimulation continued until the end of stage 12 or induction of sustained monomorphic ventricular tachycardia lasting for more than 30 seconds or requiring termination before then due to haemodynamic compromise. Reproducibility was checked if the arrhythmia could be terminated by pacing, but not if a DC shock was required.

If ventricular tachycardia could be induced, conventional drug testing was performed at the end of the research study. A single intravenous dose of an appropriate antiarrhythmic agent was administered and programmed ventricular stimulation repeated. Plasma drug concentrations were then checked 48 hours later just before the next study to confirm complete removal.

STATISTICS

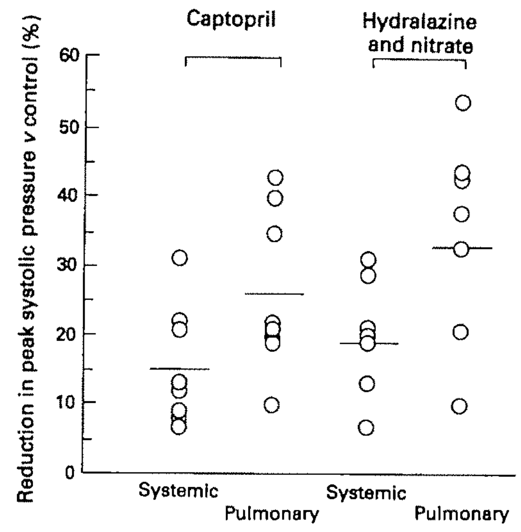
Continuous variables are given as mean (SD) and have been compared between the three treatment periods by multiple paired *t* tests, assuming the absence of any order or period effect. Values of $p < 0.05$ were regarded as significant. Changes in the stage at which ventricular tachycardia could be induced were assessed by the sign test.

Results

Seven patients completed all three treatment periods but one patient (No 6) was withdrawn at his own request after the captopril and control limbs. The final doses of vasodilator were captopril, 12·5 mg ($n = 1$), 25 mg ($n = 6$), 50 mg ($n = 1$) and hydralazine combined with isosorbide mononitrate, 50 mg and 10 mg ($n = 5$) and 100 mg and 20 mg ($n = 2$). Six patients complained of headache during hydralazine and nitrate treatment but there were no other adverse effects. Table 1 shows clinical data from the patients.

HAEMODYNAMIC CHANGES

Compared with the control period, both captopril and hydralazine combined with nitrate produced significant reductions in mean arterial and pulmonary artery pressure, with a fall in systemic vascular resistance and a rise in cardiac index (table 2). As expected, both vasodilator regimens elicited similar, balanced reductions in afterload and preload. The figure shows the mean (range) fall in peak systolic blood pressure compared with the control period. This was 15 (7–30)% with captopril and 19 (7–31)% with hydralazine and nitrate. The corresponding reductions in peak systolic pulmonary artery pressure were 26 (10–43)% for captopril and 33 (10–54)% for hydralazine and nitrate. Captopril lowered pulmonary capillary wedge pressure by 6 (1–12) mm Hg and right atrial pressure by 3 (–1 to 6) mm Hg, whereas hydralazine and nitrate reduced wedge pressure by 10 (5–18) mm Hg and right atrial pressure by 5 (1–12) mm Hg. Although the haemodynamic changes were somewhat greater with hydralazine and nitrate compared with captopril, these differences did not reach statistical significance.



Percentage reduction in systemic and pulmonary arterial peak systolic pressure during treatment with captopril or a combination of hydralazine and nitrate compared with the control period. Horizontal bars represent mean values.

Table 2 Changes in haemodynamic variables

	Control (n=8)	*HYD/ISMN (n=7)*	*CAPT (n=8)*
Heart rate (beats/min)	68 (14)	81 (17)	72 (14)
MAP (mm Hg)	98 (18)	83 (14)†	84 (9)†
PA (mm Hg)	28 (5)	18 (7)†	21 (6)†
RA (mm Hg)	10 (6)	5 (5)	8 (5)
PCWP (mm Hg)	20 (4)	9 (4)†	14 (3)†
CI (l/min/m^2)	2·1 (0·4)	3·0 (0·6)†	2·4 (0·4)*
SVR (dyn.s.cm^{-5})	1925 (529)	1164 (204)†	1421 (340)†
PVR (dyn.s.cm^{-5})	197 (118)	110 (81)*	139 (81)
SVI (ml/beat/m^2)	30·4 (10·7)	35·3 (6·5)	34·1 (10·5)
SWI (g × m/m^2)	32·8 (14·0)	35·7 (12·4)	32·9 (12·4)

All values are mean (SD). *$p < 0.005$ *v* control; †$p < 0.01$ *v* control. HYD, hydralazine; ISMN, isosorbide mononitrate; CAPT, captopril; MAP, mean arterial pressure; PA, mean pulmonary artery pressure; RA, mean right atrial pressure; PCWP, mean pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SVI, stroke volume index; SWI, stroke work index.

ELECTROPHYSIOLOGICAL CHANGES

Table 3 summarises the electrophysiological changes. Compared with the control period, hydralazine and nitrate produced non-significant shortening of sinus cycle length, QRS duration, and uncorrected QT interval. By contrast, captopril resulted in slight but significant prolongation of mean QT interval during atrial pacing (500 ms cycle length) from 352 to 358 ms, whereas it was unchanged during treatment with hydralazine and nitrate. Atrial refractoriness was similar during all three treatment periods, but captopril caused significant prolongation of ventricular effective and functional refractory periods compared with both the control period and treatment with hydralazine combined with nitrate.

PROGRAMMED STIMULATION

Table 4 shows the results of programmed ventricular stimulation. Ventricular tachycardia was induced in all eight patients during the control period, in seven out of eight patients during captopril treatment, and seven out of seven patients during treatment with hydralazine and nitrate. There was no significant difference in the stage at which tachycardia could be induced during any of the three limbs.

Table 3 Mean (SD) changes in electrophysiological variables

Parameter (ms)	*Control (n=8)*	*HYD/ISMN (n=7)*	*CAPT (n=8)*
SCL	885 (265)	741 (195)	837 (193)
QRS	117 (24)	111 (18)	121 (24)
QT	399 (61)	379 (44)	396 (40)
QT$_{500}$	351 (28)	352 (26)	358 (25)*
AERP	223 (35)	208 (24)	219 (34)
AFRP	256 (29)	248 (29)	256 (34)
VERP	231 (26)	228 (31)	249 (23)†
VFRP	265 (24)	252 · (29)	277 (27)*

*$p < 0{\cdot}05$, captopril *v* control; †$p < 0{\cdot}02$, captopril *v* control.
HYD, hydralazine; ISMN, isosorbide mononitrate; CAPT, captopril; SCL, sinus cycle length; QRS, QRS duration; QT, QT interval during sinus rhythm; QT$_{500}$, QT interval during atrial pacing at 500 ms cycle length; AERP, atrial effective refractory period; AFRP, atrial functional refractory period; VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period.

Table 4 Results of programmed ventricular stimulation

Patient No	*Control*	*HYD/ISMN*	*CAPT*
1	8	5	10
2	8	10	12
3	6	9	Non-inducible
4	8	6	4
5	4	4	4
6	8	Withdrew	11
7	2	2	2
8	12	11	12

Values represent stage of programmed stimulation protocol at which sustained ventricular tachycardia was induced (see methods).
HYD, hydralazine; ISMN, isosorbide mononitrate; CAPT, captopril.

Treatment with vasodilator had no effect on the cycle length or haemodynamic stability of induced ventricular tachycardia.

Discussion

We have shown that captopril caused an increase in ventricular functional and effective refractory periods with some prolongation of the paced QT interval, whereas an equivalent degree of load manipulation by hydralazine and nitrate resulted in no significant changes. The electrophysiological alterations produced by a vasodilator drug may represent a complex interaction of mechano-electrical effects due to reduction of myocardial wall stress, reflex changes in autonomic neural input, and direct effects on cardiac myocytes. In vitro research has shown that angiotensin II facilitates intraventricular conduction by increasing sodium current[11] and decreasing intercellular coupling resistance,[19] whereas captopril directly reduces membrane conductance through L type calcium channels,[12] but neither of these mechanisms would account for the electrophysiological changes seen with ACE inhibition in our study. Prolongation of ventricular refractoriness and repolarisation by captopril would be consistent with contraction excitation feedback,[8,9] and a possible explanation for the lack of change with the hydralazine and nitrate combination might lie in the differing effects of these drugs on reflex autonomic response to the fall in arterial pressure. Normally, this is accompanied by a baroreceptor mediated surge in sympathetic discharge that tends to shorten cardiac action potential duration independently of heart rate and offsets any prolongation due to contraction excitation feedback.[20] Adrenergic neurotransmission is, however, inhibited by ACE inhibitors.[10,21] This has the effect of restraining reflex sympathetic stimulation. In a comparative haemodynamic study, Daly *et al* showed that short-term administration of captopril to patients with congestive heart failure caused no change in net transmyocardial noradrenaline release, whereas a similar reduction in blood pressure by hydralazine and nitrate combination was accompanied by a noticeable increase in noradrenaline overflow.[22] Thus it is possible that any mechanically induced change in myocardial excitability during the hydralazine and nitrate treatment period may have been masked by an opposing electrophysiological effect due to the compensatory rise in cardiac sympathetic tone. Although neurohormonal measurements were not taken, hydralazine and nitrate combination did accelerate mean heart rate from 68 to 81 beats/min ($p = 0{\cdot}075$), whereas there was virtually no change with captopril.

The electrophysiological effects elicited by captopril would generally be expected to exert some antiarrhythmic influence but, disappointingly, there was no significant change in the ability to induce ventricular tachycardia. Spontaneous day to day variability of ventricular tachycardia induction by programmed stimulation may, however, prevent detection of a moderate but clinically relevant antiarrhythmic effect in such a small sample of patients.[23]

PREVIOUS STUDIES

There is now abundant evidence that the human myocardium exhibits the property of contraction excitation feedback. Ford and Campbell reported that afterload reduction by amyl nitrate is associated with QT interval prolongation.[24] More recently, Taggart *et al* have showed shortening of monophasic action potential duration in response to the increase in myocardial wall stress at the end of cardiopulmonary bypass.[25] This also occurs during transient aortic constriction,[26] and the release phase of the Valsalva manoeuvre.[27] Levine *et al* described similar changes in the right ventricular action potential during pulmonary balloon valvoplasty.[28] All of these investigations have involved large transient load shifts and less data exist on the electrophysiological effects of sustained load manipulation by vasodilator drugs. Two recent studies have shown that administration of sodium nitroprusside to patients with impaired left ventricular function does not significantly alter ventricular refractoriness[29,30]; neither study reported the effect on QT interval or any other index of repolarisation, but Carlson *et al* found that nitroprusside infusion caused a significant rise in plasma noradrenaline concentration.[29] These results are consistent with our findings on the electrophysiological effects of hydralazine and nitrate combination and the possible confounding influence of reflex sympathetic stimulation. We are not aware of any previous human studies examining the electrophysiological properties of ACE inhibitors, but our findings generally accord with those obtained by de Langen *et al* using a closed chest pig model of chronic myocardial infarction[13]; they reported that angiotensin II infusion shortened ventricular refractoriness and facilitated induction of ventricular tachycardia by programmed stimulation, whereas intravenous captopril suppressed arrhythmias that were inducible in the drug free state. Holter monitoring studies in patients with chronic heart failure, furthermore, have consistently shown ACE inhibitors reduce the frequency of asymptomatic ventricular arrhythmias.[16 17]

CLINICAL IMPLICATIONS

Sudden death accounts for 40 to 50% of the mortality in chronic heart failure and is assumed to be triggered by malignant ventricular tachyarrhythmias in a significant proportion of cases because many patients exhibit high grade ventricular extra systoles on ambulatory monitoring[1–3]; this viewpoint is supported by analysis of Holter electrocardiographic recordings at the time of sudden death.[31] Attempts at reducing risk of sudden death with conventional antiarrhythmic drugs including amiodarone have been universally disappointing.[3–5] With growing awareness of the contribution of mechano-electrical and neural mechanisms to the pathogenesis of arrhythmias in the failing heart, there are theoretical grounds for expecting ACE inhibitors to exert a protective effect, but their impact on sudden death is still a matter of dispute. It has been widely reported that the beneficial effect of enalapril in the cooperative north Scandinavian enalapril survival study (CONSENSUS) was solely due to a reduction in deaths from progressive heart failure.[7] This trial, however, only recruited patients with refractory end stage heart failure, among whom sudden death accounts for a relatively low proportion of total mortality (only 22% of deaths in the placebo limb of CONSENSUS), and is more likely to be mediated by a bradyarrhythmic mechanism.[32] By contrast, in the captopril multicenter research group study, only one of 53 patients on active treatment died suddenly compared with eight of 52 in the placebo group.[33] Fonarow *et al* have also reported a significantly lower sudden death rate among captopril treated patients compared with patients receiving hydralazine and nitrate in a randomised trial of 106 patients with chronic heart failure.[34]

LIMITATIONS

Practical considerations imposed several restrictions on the study, which should be borne in mind. We were only able to examine the short-term electrophysiological effects of vasodilator therapy, but prolonged treatment with remodelling and reduction of venticular volumes might be required to assess the full impact of mechano-electrical feedback. Refractory periods were measured in the right ventricle, whereas the myocardial disease process and arrhythmic substrate are generally located in the left ventricle. Although similar reductions in peak systolic and filling pressures were achieved on the left and right sides of the heart, we cannot be sure that electrophysiological changes in the right ventricle accurately reflect the behaviour of diseased myocardium in the infarct border zone. Also changes in myocardial wall stress during the drive train preceding the extrastimulus may make it more difficult to assess the impact of pharmacologically induced load reduction on ventricular refractoriness. This problem could be avoided by using atrial pacing to stabilise the heart rate coupled to delivery of single ventricular extrastimuli. The use of oral rather than intravenous testing prevented us from assessing the effects of load manipulation on the endocardial monophasic action potential, a more sensitive and reliable index of ventricular repolarisation than the surface QT interval.

CONCLUSIONS

We showed that load manipulation by captopril but not a hydralazine and nitrate combination prolongs ventricular refractoriness and repolarisation in patients with impaired ventricular function, possibly due to the combination of mechano-electrical feedback with inhibition of reflex sympathetic stimulation. To answer some of the questions raised, we are conducting a further study with neurohormonal monitoring and intravenous drug administration to enable recording of changes in cardiac action potential and to avoid the confounding influence of day to day variation in the ability to induce ventricular arrhythmias. Despite these limitations, the results of the present study support the use of ACE inhibitors rather than direct vasodilators as one component of a pharmacological strategy to prevent sudden arrhythmic deaths associated with impaired ventricular function.

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1 Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;72:681–5.

2 Bigger JT. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. *Circulation* 1987; 75(suppl IV):28–35.

3 Francis GS. Should asymptomatic ventricular arrhythmias in patients with congestive heart failure be treated with antiarrhythmic drugs? *J Am Coll Cardiol* 1988;12:274–83.

4 CAST Investigators. Preliminary report of the effect of flecainide and encainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.

5 Stewart RA, McKenna WJ, Poloniecki JD, Michelson JK, Das SK, Morady F, *et al*. Prospective randomized double-blind placebo-controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular ectopy [abstract]. *Eur Heart J* 1989;10(suppl): 1158.

6 Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, *et al*. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;314:1547–52.

7 CONSENSUS trial study group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429–35.

8 Lab MJ. Contraction-excitation feedback in myocardium: physiological basis and clinical relevance. *Circ Res* 1982; 50:757–66.

9 Dean JW, Lab MJ. Arrhythmia in heart failure: role of mechanically induced changes in electrophysiology. *Lancet* 1989;i:1309–12.

10 Clough DP, Collis MG, Conway J, Hatton R, Keddie JR. Interaction of angiotensin-converting enzyme inhibitors with the function of the sympathetic nervous system. *Am J Cardiol* 1982;49:1410–3.

11 Moorman JR, Kirsch GE, Lacerda AE, Brown AM. Angiotensin II modulates cardiac sodium channels in neonatal rat. *Circ Res* 1989;65:1804–9.

12 Bryant SM, Ryder KO, Hart G. Effects of captopril on

membrane current and contraction in single ventricular myocytes from guinea-pig. *Br J Pharmacol* 1991;102: 462–6.

13 de Langen CDJ, de Graeff PA, van Gilst WH, Bel KJ, Kingma JH, Wesseling H. Effects of angiotensin II and captopril on inducible sustained ventricular tachycardia two weeks after myocardial infarction in the pig. *J Cardiovasc Pharmacol* 1989;13:186–91.

14 Dean JW, Lab MJ. Regional changes in ventricular excitability during load manipulation of the in situ pig heart. *J Physiol* 1990;429:387–400.

15 Bussman WD, Neuman K, Kaltenbach M. Effect of intravenous nitroglycerin on ventricular ectopic beats in acute myocardial infarction. *Am Heart J* 1984;107:940–4.

16 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, *et al.* Captopril in heart failure—a double-blind controlled trial. *Br Heart J* 1984;52:530–5.

17 Webster MWI, Fitzpatrick A, Nicholls MG, Ikram H, Wells JE. Effect of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol* 1985;56:566–9.

18 Grossman W. *Cardiac catheterisation and angiography*. 3rd ed. Philadelphia: Lea and Febiger, 1986:135–42.

19 Hermsmeyer K. Angiotensin II increases electrical coupling in mammalian ventricular myocardium. *Cir Res* 1980;47: 524–9.

20 Davidowski TA, Wolf S. The QT interval during reflex cardiovascular adaptation. *Circulation* 1984;69:22–5.

21 McCance AJ, Forfar JC. Whole body norepinephrine kinetics in patients with chronic heart failure treated with ramipril [abstract]. *J Am Coll Cardiol* 1991;17:162.

22 Daly P, Rouleau JL, Cousineau D, Burgess JH, Chatterjee K. Effects of captopril and a combination of hydralazine and isosorbide dinitrate on myocardial sympathetic tone in patients with severe congestive heart failure. *Br Heart J* 1986;56:152–7.

23 Cooper MJ, Koo CC, Skinner MP, Mortensen PT, Hunt LJ, Richards DA, *et al.* Comparison of immediate versus day-to-day variability of ventricular tachycardia induction by programmed stimulation. *J Am Coll Cardiol* 1989;13:1599–607.

24 Ford EL, Campbell NP. Effect of myocardial shortening velocity on duration of electrical and mechanical systole. *Br Heart J* 1980;44:179–83.

25 Taggart P, Sutton PMI, Treasure T, Lab MJ, O'Brien W, Runnalls M, *et al.* Monophasic action potentials at discontinuation of cardiopulmonary bypass: evidence for contraction-excitation feedback in man. *Circulation* 1988; 77:1266–75.

26 Taggart P, Sutton PMI, Lab MJ, Runnalls M, O'Brien W, Treasure T. Beat-to-beat response of repolarization to transient aortic occlusion in man [abstract]. *Eur Heart J* 1990;11(suppl):42.

27 Taggart P, Sutton PMI, John R, Lab MJ, Swanton RH. Interaction between cycle length and ventricular loading conditions on repolarization [abstract]. *Eur Heart J* 1990; 11(suppl):42.

28 Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Changes in myocardial repolarization in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction-excitation feedback in humans. *Circulation* 1988;77:70–7.

29 Carlson MD, Schoenfeld MH, Garan H, Choong CY, Davidoff R, Weyman AE, *et al.* Programmed ventricular stimulation in patients with left ventricular dysfunction and ventricular tachycardia: effects of acute haemodynamic improvement due to nitroprusside. *J Am Coll Cardiol* 1989;14:1744–52.

30 Kulick DL, Bhandari AK, Hong R, Petersen R, Leon C, Rahimtoola S. Effect of acute haemodynamic decompensation on electrical inducibility of ventricular arrhythmias in patients with dilated cardiomyopathy and complex non-sustained ventricular arrhythmias. *Am Heart J* 1990;119:878–83.

31 de Luna AB, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; 117:151–9.

32 Luu M, Stevenson WG, Stenson LW, Baron K, Warden J. Diverse mechanisms of unexpected cardiac arrests in advanced heart failure. *Circulation* 1989;80:1675–80.

33 Dennick LG, Maskin CS, Meyer JH, Schotz WE, Brown BW. Enalapril for congestive heart failure [letter]. *N Engl J Med* 1987;317:1350.

34 Fonarow G, Chelimsky-Fallick C, Stevenson LW, Stevenson WG, Luu M, Hamilton MA, *et al.* Impact of vasodilator regimen on sudden death in advanced heart failure: a randomised trial of angiotensin-converting-enzyme inhibition and direct vasodilation [abstract]. *J Am Coll Cardiol* 1991;17:92.

Br Heart J 1992;67:361–7

Role of atrial contraction and synchrony of ventricular contraction in the optimisation of ventriculoarterial coupling in humans

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Abstract

***Objective*—To examine the effects of pacing modes on the interaction between the left ventricle and arterial system in humans.**

***Design*—The slope of the end systolic pressure-volume relation (end systolic elastance), effective arterial elastance, the ratio of effective arterial elastance to end systolic elastance, and mechanical energy efficiency were compared under different pacing modes (atrial, atrioventricular, and ventricular).**

***Patients*—Nine male patients with sick sinus syndrome who had cardiac catheterisation for diagnosis and to see whether they needed a pacemaker.**

***Interventions*—A conductance catheter with tip-manometer was inserted into the left ventricle to obtain pressure-volume loops, and two pacing catheters were inserted into the right atrium and into the right ventricle respectively.**

***Results*—End systolic elastance was lower in atrioventricular pacing than in atrial pacing, but effective arterial elastance was not significantly different. End systolic elastance was lower in ventricular pacing than in atrioventricular pacing, and effective arterial elastance was higher in ventricular pacing than in atrioventricular pacing. Consequently the ratio of effective arterial elastance to end systolic elastance was lowest in atrial pacing and highest in ventricular pacing, and mechanical energy efficiency was highest in atrial pacing and lowest in ventricular pacing.**

***Conclusions*—Atrial contraction and synchronous ventricular contraction independently optimise ventriculoarterial coupling in terms of a transfer of energy. Thus atrial pacing gives the best ventriculo-arterial coupling among these pacing modes.**

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Pacemaker implantation is now widely used to treat bradycardia. The synchrony of ventricular contraction during atrial pacing differs from that during atrioventricular and ventricular pacing. Atrioventricular pacing produces atrial contraction whereas ventricular pacing does not. Previous studies showed the benefits of physiological pacing over ventricular pacing in terms of haemodynamic function—that is, cardiac output, arterial pressure, etc.[1-3] However, the interaction between the left ventricle and arterial system (ventriculoarterial coupling) has not yet been studied. The assessment of ventriculoarterial coupling is particularly important because the nature of the coupling of the left ventricle to the arterial system determines the efficiency of energy transfer to the circulation and is a major determinant of ventricular and circulatory performance.[4-6]

A conductance catheter with tip manometer[7-9] can be used to obtain left ventricular pressure-volume loops on a beat-to-beat basis and to show the end systolic pressure-volume relation. On the pressure-volume diagram the slope of the end systolic pressure-volume relation (end systolic elastance)[10-12] and effective arterial elastance[13 14] can be simultaneously determined to assess ventriculoarterial coupling. Furthermore, the pressure-volume diagram provides an estimate of mechanical energy efficiency—that is, the ratio between work area and the pressure-volume area, because the pressure-volume area is linearly related to ventricular oxygen consumption.[4]

We used a conductance catheter to assess the effect of pacing modes on the interaction between the left ventricle and arterial system.

Patients and methods

PATIENTS

We studied nine men (44–64 (mean 55)) with sick sinus syndrome. All of them had cardiac catheterisation for diagnosis and to decide whether they needed a pacemaker. Left ventriculography and coronary angiography showed no ventricular wall motion abnormality or coronary artery disease in any of the patients. None showed evidence of aortic or mitral regurgitation or left ventricular hypertrophy on the left ventriculogram and echocardiogram.

All patients gave informed consent to diagnostic catheterisation and participation in the study protocol. The protocol was approved by the Osaka Police Hospital Ethical Committee.

PRESSURE AND VOLUME MEASUREMENT

A conductance catheter with a manometer at its tip was inserted into the left ventricle. This catheter was connected to a volumetric system (Model Sigma 5, Leycom, Oegstgeest, The Netherlands) to convert left ventricular conductance to left ventricular volume. The position of the catheter in the left ventricle was confirmed by the presence of a signal with a flat upper segment or identity of the phase of the signal among the segments. The catheter technique for measurement of left ventricular volume has been described in detail elsewhere.[7 8 15] In brief, the instantaneous left ventricular volume, V(t), was obtained by the Sigma 5 as:

$$V(t) = (1/a)(L^2/B)G(t) - Vc \qquad (1)$$

where a is a dimensionless constant, L is an interelectrode distance, B is the specific conductivity of blood measured by a calibrating cuvette, and G(t) is the sum of the segmental conductance measured between the five pairs of adjacent electrodes. Vc is the correction volume for the parallel conductance.

The so-called dilution method was used to obtain the correction volume, Vc. A bolus of hypertonic salt solution (6% NaCl) of 10 ml was injected into pulmonary artery through a balloon-tipped flotation thermodilution catheter. As the salt solution mixed with blood in the left ventricle its conductivity (B in equation (*1*)) increased, causing the overall conductance signal G(t) to increase while the parallel component remained constant. When measured end systolic volume was plotted as a function of measured end diastolic volume during the mixing of the bolus and linear regression analysis was applied to the relation between measured end systolic volume and measured end diastolic volume data points, the intersection point between the regression line and the line of identity was Vc, the correction volume.[7]

To determine a in equation (*1*) the stroke volume was simultaneously measured by the thermodilution method and by a conductance catheter.[15]

$$\text{Actual stroke volume} = (1/a)(L^2/B)(G(ed) - G(es))$$

$$(1/a) = \text{actual stroke volume}/(L^2/B)/(G(ed) - G(es))$$

where the actual stroke volume is the stroke volume measured by the thermodilution method, G(ed) is the sum of the segmental end diastolic conductance, and G(es) is the sum of the segmental end systolic conductance.

Good correlations between left ventricular volumes measured by the conductance catheter and by other methods have been shown both by us[16] and others.[7 17 18] The signals of left ventricular volume and pressure were sampled every 5 ms and analysed on a personal computer (NEC 9800 (NEC, Japan)).

EVALUATION OF THE END SYSTOLIC PRESSURE-VOLUME RELATION

To measure the end systolic pressure-volume relation, the inferior vena cava was obstructed with the Fogarty catheter to reduce peak systolic pressure by 15–40%. A maximum pressure-volume ratio point—that is, the peak value of the ratio of left ventricular pressure to left ventricular volume within cardiac cycle—was calculated over eight seconds during occlusion of the inferior vena cava. Linear regression analysis of these points was used to determine the end systolic pressure-volume relation,[19] and end systolic elastance was used as an index of cardiac contractility.[10–12]

EVALUATION OF EFFECTIVE ARTERIAL ELASTANCE

Effective arterial elastance can be determined in the pressure-volume diagram as the ratio of end systolic pressure to stroke volume[13 14]:

$$Ea = Pes/SV = (Rc + R)/T \qquad (2)$$

where Ea is the effective arterial elastance, Pes the left ventricular end systolic pressure, SV the stroke volume, Rc the characteristic impedance, R the arterial resistance, and T the duration of one cardiac cycle.

In this study, heart rate was fixed at 90 beats per minute to keep T in equation (*2*) constant; therefore, effective arterial elastance changed in parallel with the total arterial elastance.

EVALUATION OF MECHANICAL ENERGY EFFICIENCY

Mechanical energy efficiency was determined as the ratio of external work to pressure-volume area by the following equation,[4 5]

$$\text{Mechanical energy efficiency} = \text{external work}/\text{pressure-volume area}$$

The pressure-volume area, which was determined as the area surrounded by the line of the end systolic pressure-volume relation, the end diastolic pressure-volume curve, and the systolic segment of the pressure-volume trajectory, represents the total mechanical energy of the ejecting contraction.[4] External work was measured as the area enclosed by a pressure-volume loop.

PACING STUDY

Two bipolar pacing catheters were introduced through the femoral vein and positioned in the right atrial appendage and the right ventricular apex, respectively. Pressure-volume loops and end systolic pressure-volume relations were obtained during atrial, atrioventricular, and ventricular pacing with a constant heart rate of 90 beats per minute when the inferior vena cava was occluded. The pacing modes were changed in a random order. Data were recorded five minutes after the pacing mode was changed. During ventricular pacing the atrium was paced 50 ms after the ventricle to exclude the contribution of random atrial contraction to left ventricular filling. During atrioventricular pacing the atrioventricular delay was 150 ms.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). The statistical significance of differences in the indices among pacing modes was tested by an analysis of variance (ANOVA) and Scheffe's F test. Results were regarded as significant when $p < 0{\cdot}05$.

Results

Figure 1 shows representative pressure-volume loops for each pacing mode. Panel A shows pressure-volume loops and end systolic

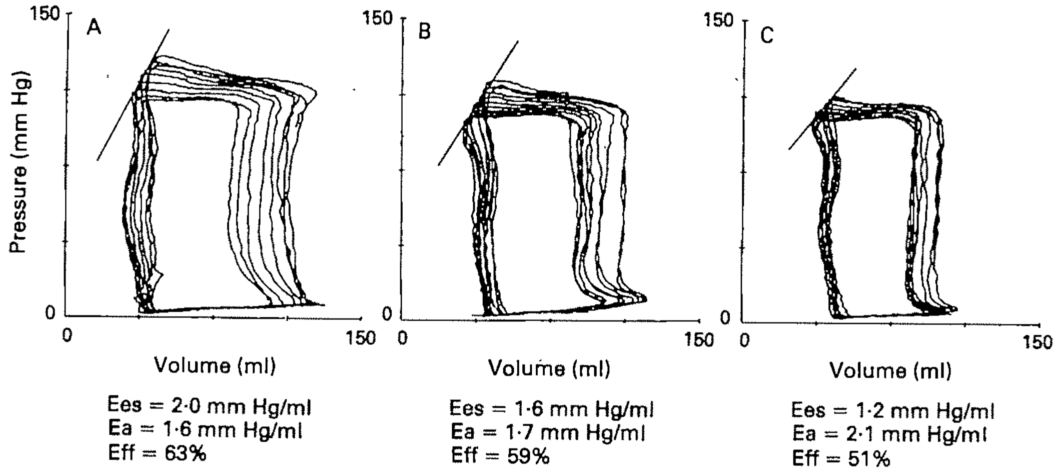

Figure 1 Representative pressure-volume loops obtained at atrial pacing (A), atrioventricular pacing (B), and ventricular pacing (C). End systolic elastance (Ees) and mechanical energy efficiency (Eff) were lower and effective arterial elastance (Ea) was higher during ventricular pacing than during atrioventricular pacing. Ees and Eff were lower during atrioventricular pacing than during atrial pacing.

pressure-volume relations obtained during occlusion of the inferior vena cava and atrial pacing. End systolic elastance and mechanical energy efficiency were lower during atrioventricular pacing than during atrial pacing (B). End systolic elastance and mechanical energy efficiency were lower and effective arterial elastance was higher in ventricular pacing than in atrioventricular pacing (C).

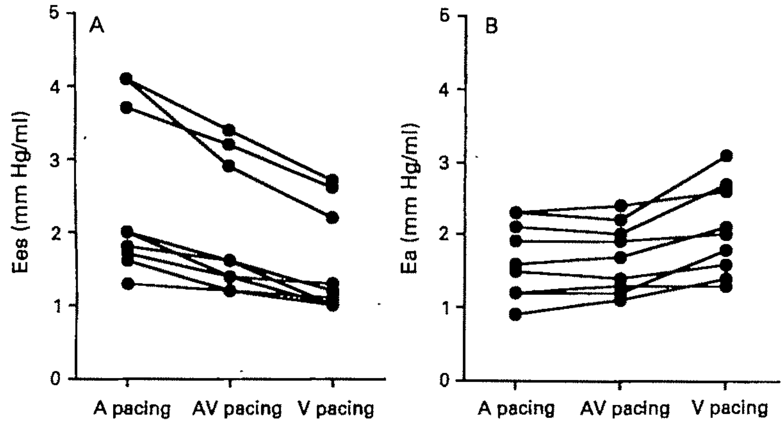

Figure 2 (A) Changes in end systolic elastance (Ees) during atrial (A) pacing, atrioventricular (AV) pacing, and ventricular (V) pacing. Ees during atrial pacing was significantly higher than during atrioventricular pacing ($p < 0\cdot01$). Ees during atrioventricular pacing was higher than during ventricular pacing ($p < 0\cdot05$).
(B) Changes in effective arterial elastance (Ea) during atrial pacing, atrioventricular pacing and ventricular pacing. Ea was similar during atrial pacing and atrioventricular pacing. However, Ea was higher during ventricular pacing than during atrioventricular pacing ($p < 0\cdot01$).

Haemodynamic variables (mean (SD)) in the three pacing modes

Variable	*Atrial pacing*	*AV pacing*	*Ventricular pacing*
LVESVI (ml/m^2)	24 (7)	23 (8)	23 (7)
LVEDVI (ml/m^2)	69 (11)	66 (10)	55 (11)**††
SVI (ml/m^2)	46 (8)	43 (5)	32 (6)**††
LVESP (mm Hg)	132 (27)	130 (25)	113 (17)**††
Ees (mm Hg/ml)	2·5 (1·1)	2·0 (0·9)**	1·6 (0·7)**†
Ea (mm Hg/ml)	1·7 (0·5)	1·7 (0·5)	2·1 (0·6)**††
Ea/Ees	0·72 (0·18)	0·92 (0·22)*	1·41 (0·29)**††
Eff (%)	68 (8)	63 (9)**	56 (8)**††

*$p < 0\cdot05$ and **$p < 0\cdot01$ versus atrial pacing; †$p < 0\cdot05$ and ††$p < 0\cdot01$ versus atrioventricular pacing.
AV, atrioventricular; Ea, effective arterial elastance; Ees, end systolic elastance; Eff, mechanical energy efficiency; LVEDVI, left ventricular end diastolic volume index; LVESP, left ventricular end systolic pressure; LVESVI, left ventricular end systolic volume index; SVI, stroke volume index.

LEFT VENTRICULAR PRESSURE AND VOLUME CHANGES

Left ventricular volume index and pressure were not significantly different during atrial pacing and during atrioventricular pacing. Left ventricular end diastolic volume index and left ventricular end systolic pressure were smaller during ventricular pacing than during atrioventricular pacing ($p < 0\cdot01$). Left ventricular end systolic volume indices during these two pacing modes were not significantly different. Consequently, stroke volume index was significantly smaller during ventricular pacing than during atrioventricular pacing (table).

CHANGES IN VENTRICULOARTERIAL COUPLING AND MECHANICAL ENERGY EFFICIENCY

End systolic elastance was 16% lower during atrioventricular pacing than during atrial pacing (fig 2A) ($p < 0\cdot01$) and effective arterial elastance was similar during both modes (fig 2B). Therefore, the mean ratio of effective arterial elastance to end systolic elastance was greater (fig 3A) and mechanical energy efficiency was smaller (fig 3B) during atrioventricular pacing than during atrial pacing.

During ventricular pacing end systolic elastance was lower ($p < 0\cdot05$) (fig 2A) and effective arterial elastance was 23% higher ($p < 0\cdot01$) than during atrioventricular pacing (fig 2B). Thus the mean ratio of effective arterial elastance to end systolic elastance was greater (fig 3A) and mechanical energy efficiency was less (fig 3B) during ventricular pacing than during atrioventricular pacing.

Discussion

The effects of pacing modes—that is, atrial, atrioventricular, and ventricular pacing—on the interaction of the left ventricle and arterial system were assessed by the measurement of end systolic elastance and effective arterial elastance. Both atrial contraction and synchrony of ventricular contraction were important in the optimisation of ventriculoarterial coupling.

SYNCHRONY OF LEFT VENTRICULAR CONTRACTION

There was no significant difference in left ventricular volume and pressure between atrial

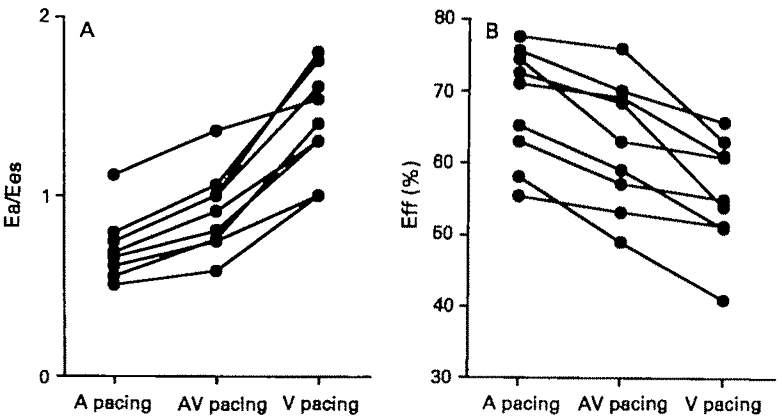

Figure 3 (A) Changes in Ea/Ees between atrial (A) pacing, atrioventricular (AV) pacing, and ventricular (V) pacing. This ratio was lowest during atrial pacing and highest during ventricular pacing. (B) Changes in Eff during atrial pacing, atrioventricular pacing, and ventricular pacing. Eff was highest during atrial pacing and lowest during ventricular pacing. See legend to fig 1 for abbreviations.

pacing and atrioventricular pacing. Therefore there was no significant difference in effective arterial elastance between these two pacing modes. End systolic elastance was lower in atrioventricular pacing than in atrial pacing. The reduction of end systolic elastance may be due to dyssynchronous ventricular contraction, because the mode of ventricular contraction—that is, synchronous or dyssynchronous—is the most important difference between these pacing modes. Badke *et al* reported that ventricular pacing promoted dyssynchronous ventricular contraction with reciprocal interactions between the early and late shortening areas.[20] At end systole those portions of the left ventricle that were activated first lengthen (whereas in the most recently activated area they shorten) and thus do not contribute to the generation of end systolic left ventricular pressure. There are several reports that areas of the left ventricle that are activated early bulge paradoxically in late systolic phase during dyssynchronous left ventricular contraction.[21-23] Furthermore, Rosenqvist *et al* showed that abnormal ventricular activation—that is, dyssynchronous ventricular contraction—results in a significant deterioration in regional left ventricular systolic performance in humans.[24] Burkhoff *et al* showed that pacing from different ventricular sites that changed the degree of dyssynchrony of ventricular contraction resulted in different intensities of ventricular performance.[25] Thus dyssynchronous ventricular contraction may well be responsible for the reduced cardiac contractility during atrioventricular pacing.

ATRIAL CONTRACTION

Left ventricular end systolic pressure was lower during ventricular pacing than during atrioventricular pacing. In addition, without atrial contraction left ventricular end diastolic volume and stroke volume also decreased. Therefore, effective arterial elastance increased during ventricular pacing, as it did in an earlier study in dogs.[26] Sympathetic stimulation, which is accompanied by a reduction of stroke volume, may be partly responsible for the increase in effective arterial elastance.

End systolic elastance was lower during ventricular pacing than during atrioventricular pacing (fig 2A). The lack of atrial contraction during ventricular pacing reduced the left ventricular end diastolic volume and changed the filling pattern.[27] In earlier studies end systolic elastance was insentitive to changes of load.[10,28] However, a rapid increase in left ventricular volume in late diastole reduced left ventricular end systolic volume and increased left ventricular end systolic pressure.[29,30] This strongly suggests that cardiac contractility is increased by a rapid increase in left ventricular volume during late diastole. In ventricular pacing, filling occurs mainly in early diastole and little filling is seen in late diastole. In contrast, early diastolic filling is equal to or even less in atrioventricular pacing than in ventricular pacing, and during atrioventricular pacing late diastolic filling is much greater, producing a rapid increase in left ventricular volume.[27] Thus the reduction of cardiac contractility in ventricular pacing may be explained by the difference in the filling pattern.

VENTRICULOARTERIAL COUPLING AND MECHANICAL ENERGY EFFICIENCY

The ratio of effective arterial elastance to end systolic elastance, the index of ventriculoarterial coupling, was lowest during atrial pacing and was highest during ventricular pacing. As a result, mechanical energy efficiency was highest in atrial pacing and lowest in ventricular pacing.

Earlier studies showed that the pressure-volume area represents the total mechanical energy generated by ventricular contraction.[4,5] The efficiency of energy transfer from ventricular oxygen consumption to external work can be divided into two steps: the efficiency of energy transfer from ventricular oxygen consumption to the pressure-volume area and the efficiency of energy transfer from pressure-volume area to external work.[31,32] The second step represents mechanical energy efficiency and we found that the efficiency of the second step was reduced by dyssynchrony of ventricular contraction and absence of atrial contraction. These results suggest that dyssynchronous ventricular contraction and absent atrial contraction waste energy and produce an energetically poor coupling between the left ventricle and the arterial system. We did not measure ventricular oxygen consumption so the effect of dyssynchronous ventricular contraction or absence of atrial contraction on the first step of energy transfer is unknown.

STUDY LIMITATION

The study population was small. The trends shown by the results were so clear, however, that we believe the conclusion of this study will not be affected by increasing the sample size.

Secondly, the end systolic pressure-volume relation in dogs was non-linear.[33-35] None the less, Kass *et al* and Little *et al* reported that end systolic elastance did approximate to a straight line over a limited load range and that this could be used to assess the inotropic state.[36,37]

We used a linear approximation of the end systolic pressure-volume relation to determine end systolic elastance in this study.

Thirdly, Boltwood *et al* reported difficulties in measuring "absolute" left ventricular volume by a conductance catheter.[38] But they also said that their data did not exclude the possibility that a conductance catheter can give a useful measurement of "relative" left ventricular volume over a range of haemodynamic states. Furthermore, the reliability of the measurement of left ventricular volume and of the end systolic pressure-volume relation by the conductance catheter has been validated by several groups,[7 39 40] and also by us.[16] Burkhoff raised some questions about Boltwood *et al's* results.[41] Thus we think that possible errors in the determination of left ventricular volumes with the conductance catheter are unlikely to affect the conclusion of our study.

Fourthly, atrioventricular delay can affect the results of this study. Iwase *et al* described the effects of atrioventricular delay on cardiac function.[42] Nitsch *et al* and Videen *et al*, however, found that changes in the atrioventricular delay in patients without ventricular dysfunction had no significant haemodynamic effects.[43 44] The haemodynamic effects of atrioventricular delay seem to depend on left ventricular function[42 45] and the interatrial conduction delay.[46] None of the patients we studied had left ventricular wall motion abnormality or coronary artery disease when they were examined by left ventriculography and coronary angiography. We examined a volume-time curve for the left atrium to ventricular sequence to determine the interatrial conduction delay. The interatrial conduction delay calculated as 150 ms minus the left atrium to ventricular sequence ranged from 76 to 97 ms (mean 86 ms) in this study, and thus the effects of interindividual difference in the interatrial conduction delay on our results are likely to be small. Furthermore, the effects of atrioventricular delay were much smaller than those of the pacing mode.[27 42 45] However, in individuals with a long interatrial conduction delay the effects of interatrial conduction delay or atrioventricular delay would not be negligible.

Fifthly, we used atrial pacing 50 ms after the ventricular stimulation to exclude varying timing of atrial contraction during the cardiac cycle in ventricular pacing. Naito *et al* and Faerestrand *et al* showed that haemodynamic function was worse after ventricular pacing with retrograde ventriculoatrial conduction than after ventricular pacing without retrograde ventriculoatrial conduction or after atrial fibrillation with regular ventricular pacing.[47 48] Naito *et al* suggested that this poor haemodynamic function when retrograde ventriculoatrial conduction was present might be explained by pulmonary venous regurgitation caused by atrial contraction during the ventricular ejection period.[47] In addition, when the atrium contracts during the ventricular ejection period various reflex mechanisms such as atrial stretch receptors and baroreceptors might influence haemodynamic function including cardiac function. Thus the differences that we found between atrioventricular and ventricular pacing may be partially attributable to the atrial pacing 50 ms after the ventricular stimulation.

Finally, we used effective arterial elastance as the index of afterload in this study and we did not take account of the influence of wave reflection in the arterial system on afterload because effective arterial elastance is developed on the basis of the three element Windkessel. Because we did not measure instantaneous arterial pressure we have no data on systemic arterial resistance and wave reflection. This precludes our assessing the relation between the changes in systemic arterial resistance and wave reflection and the changes in effective arterial elastance. However, Pepine *et al* and Murgo *et al* showed that peripheral resistance accounts for more than 90% of aortic input impedance and wave reflection for less than 5%.[49 50] Burkhoff and his colleagues showed that the Windkessel model gave a reasonable representation of afterload.[51] Sunagawa and his colleagues showed that most of the effects of afterload on stroke volume depended on peripheral resistance.[52] They also showed that effective arterial elastance correlated linearly with the ratio of total resistance (the sum of the arterial resistance and characteristic impedance) to the duration of one cardiac cycle,[53] and that the linear relation between end systolic pressure and stroke volume was seen under the same arterial impedance properties modelled in terms of a three element Windkessel.[13] Thus we think that the changes in effective arterial elastance reflected the changes in afterload, and we used such changes to assess the changes in ventriculoarterial coupling.

CLINICAL IMPLICATION

Our study showed that end systolic elastance was lower during atrioventricular pacing than during atrial pacing and that end systolic elastance was lower and effective arterial elastance was higher during ventricular pacing than during atrioventricular pacing. Therefore mechanical energy efficiency was highest in atrial pacing and lowest in ventricular pacing. We conclude that dyssynchronous ventricular contraction promotes a reduction in cardiac contractility and modifies ventriculoarterial coupling to reduce mechanical energy efficiency. A lack of atrial contraction promotes a reduction in cardiac contractility and an increase in afterload, thus modifying ventriculoarterial coupling to reduce mechanical energy efficiency. These findings show that the pacing mode influences the interaction between the left ventricle and arterial system and that an atrial contraction and synchronous ventricular contraction are important in the optimisation of ventriculoarterial coupling. Rosenqvist *et al* found a significantly higher incidence of congestive heart failure and mortality in patients with ventricular pacing than in patients with atrial pacing.[54] Alpert *et al* showed that the survival rate in patients with congestive heart failure was lower with ventricular pacing than with atrioventricular pacing.[55] Our results suggest that these earlier findings may be partially explained by inappropriate ventriculoarterial coupling in patients with ventricular pacing.

Our results show that atrial pacing gave the best ventriculoarterial coupling and mechanical energy efficiency. In patients with ventricular dysfunction, optimisation of ventriculoarterial coupling is important because it is a determinant for external work. Burkhoff and Sagawa showed that stroke work is greatest when end systolic elastance equals effective arterial elastance.[56] In patients with ischaemic heart disease optimisation of mechanical energy efficiency is important because blood supply is limited by coronary artery stenoses. Furthermore, dyssynchronous ventricular contraction had a deleterious effect on left ventricular relaxation.[57,58] Thus atrial pacing is especially suitable for patients with ventricular dysfunction and/or ischaemic heart disease. If possible, the atrioventricular delay should be prolonged in patients with atrioventricular pacing to obtain synchronous ventricular contraction.

This study also showed the advantage of assessing ventriculoarterial coupling in individual patients. For example, during ventricular pacing end systolic pressure was lowest, but "real afterload"—that is, effective arterial elastance—was highest because of the further reduction of stroke volume. During atrioventricular pacing left ventricular volume indices and pressure were not significantly different from those at atrial pacing; however, end systolic elastance—that is, the index of cardiac contractility—was smaller in atrioventricular pacing. Thus the assessment in terms of ventriculoarterial coupling gives more detailed information about the most suitable pacing mode in individual patients.

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1 Reiter MJ, Hindman MC. Hemodynamic effects of acute atrioventricular sequential pacing in patients with left ventricular dysfunction. *Am J Cardiol* 1982;49:687–92.
2 Kruse I, Arnman K, Conradson TB, Ryden L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1982;65:846–55.
3 Koretsune Y, Kodama K, Nanto S, *et al.* The effect of pacing mode on external work and myocardial oxygen consumption. In: Steinbach K, ed. *Cardiac pacing*. Darmstadt: Steinkopff Verlag, 1983:181–6.
4 Suga H. Total mechanical energy of a ventricle model and cardiac oxygen consumption. *Am J Physiol* 1979;236: H498–505.
5 Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H. Efficiency of energy transfer from pressure-volume area to external mechanical work increases with contractile state and decreases with afterload in the left ventricle of the anesthetized closed-chest dog. *Circulation* 1988;77:1116–24.
6 Asanoi H, Sasayama S, Kameyama T. Ventriculoarterial coupling in normal and failing heart in humans. *Circ Res* 1989;65:483–93.
7 Baan J, Van der Velde ET, De Bruin HG, *et al.* Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984;70: 812–23.
8 Baan J, Jong TTA, Kerkhof PLM, *et al.* Continuous stroke volume and cardiac output from intraventricular dimensions obtained with impedance catheter. *Cardiovasc Res* 1981;15:328–334.
9 McKay RG, Spears JR, Aroesty JM, *et al.* Instantaneous measurement of left and right ventricular stroke volume and pressure-volume relationships with an impedance catheter. *Circulation* 1984;69:703–10.
10 Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and the effects of epinephrine and heart rate on the ratio. *Circ Res* 1973;32:314–22.
11 Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* 1974;35:117–26.
12 Grossman W, Braunwald E, Mann T, McLaurin LP, Green LH. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. *Circulation* 1977;56:845–52.
13 Sunagawa K, Maughan WL, Burkhoff D. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983;245:H773–80.
14 Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res* 1985;56:586–95.
15 Kass DA, Midel M, Graves W, Brinker JA, Maughan WL. Use of a conductance (volume) catheter and transient inferior vena caval occlusion for rapid determination of pressure-volume relationships in man. *Cathet Cardiovasc Diagn* 1988;15:192–202.
16 Yamamoto K, Kodama K, Masuyama T, *et al.* Adverse effects of epinephrine in patients with advanced left ventricular dysfunction: analysis of ventriculo-arterial coupling. *Int J Cardiol* 1992;32:143–55.
17 Burkhoff D, Van der Velde E, Kass D, Baan J, Maughan WL, Sagawa K. Accuracy of volume measurement by conductance catheter in isolated ejecting canine hearts. *Circulation* 1985;72:440–7.
18 Applegate RJ, Cheng CP, Little WC. Simultaneous conductance catheter and dimension assessment of left ventricle volume in the intact animal. *Circulation* 1990;81:638–48.
19 Kono A, Maughan WL, Sunagawa K, Hamilton K, Sagawa K, Weisfeldt ML. The use of left ventricular end-ejection pressure and peak pressure in the estimation of the end-systolic pressure-volume relationship. *Circulation* 1984; 70:1057–65.
20 Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. *Am J Physiol* 1980;238:H858–67.
21 Hood WB Jr, Joison J, Abelmann WH, Norman JC. Asynchronous contraction due to late systolic bulging at left ventricular pacing sites. *Am J Physiol* 1969;217: 215–21.
22 Miyazawa K, Arai T, Shirato K, *et al.* Regional contraction patterns of the left ventricle during ventricular pacing. *Tohoku J Exp Med* 1977;122:167–74.
23 Little WC, Reeves RC, Arciniegas J, Katholi RE, Rogers EW. Mechanism of abnormal interventricular septal motion during delayed left ventricular activation. *Circulation* 1982;65:1486–91.
24 Rosenqvist M, Isaaz K, Botvinick EH, *et al.* Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. *Am J Cardiol* 1991;67:148–56.
25 Burkhoff D, Oikawa RY, Sagawa K. Influence of pacing site on canine left ventricular contraction. *Am J Physiol* 1986;251:H428–35.
26 Zhou JT, Yu GY. Hemodynamic findings during sinus rhythm, atrial and AV sequential pacing compared to ventricular pacing in a dog model. *PACE* 1987;10:118–24.
27 Masuyama T, Kodama K, Uematsu M, *et al.* Beneficial effects of atrioventricular sequential pacing on cardiac output and left ventricular filling assessed with pulsed Doppler echocardiography. *Jpn Circ J* 1986;50:799–807.
28 Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure/volume ratio: a new index of ventricular contractility. *Am J Cardiol* 1977;40:748–53.
29 Kil PJM, Schiereck P. End-systolic pressure-volume relations of isolated ejecting rabbit left ventricles after quick diastolic volume changes. *Cardiovasc Res* 1985;19:782–92.
30 Van Hessen MWJ, Schiereck P, Stokhof AA, *et al.* Effect of timing of transient diastolic changes in ventricular filling on LV performance in dogs. *Am J Physiol* 1989;257: H305–13.
31 Suga H, Hayashi T, Shirahata M. Ventricular systolic pressure-volume area as predictor of cardiac oxygen consumption. *Am J Physiol* 1981;240:H39–44.
32 Suga H, Hisano R, Goto T, Yamada O, Igarashi Y. Effect of positive inotropic agents on the relation between oxygen consumption and systolic pressure volume area in canine left ventricle. *Circ Res* 1983;53:306–18.
33 Burkhoff D, Sugiura S, Yue DT, Sagawa K. Contractility-dependent curvilinearity of end-systolic pressure-volume relations. *Am J Physiol* 1987;252:H1218–27.
34 Freeman GL, Little WC, O'Rourke RA. The effect of vasoactive agents on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. *Circulation* 1986;74:1107–13.
35 Suga H, Yamada O, Goto Y, Igarashi Y. Peak isovolumic pressure-volume relation of puppy left ventricle. *Am J Physiol* 1986;250:H167–72.
36 Kass DA, Beyar R, Landkford E, Heard M, Maughan WL, Sagawa K. Influence of contractile state on curvilinearity of in situ end-systolic pressure-volume relations. *Circulation* 1989;79:167–78.
37 Little WC, Cheng C-P, Peterson T, Vinten-Johansen J. Response of the left ventricular end-systolic pressure-volume relation in conscious dogs to a wide range of contractile state. *Circulation* 1988;78:736–45.
38 Boltwood CM Jr, Appleyard RF, Glantz SA. Left ventricular volume measurement by conductance catheter in intact dogs: parallel conductance volume depends on left ventricular size. *Circulation* 1989;80:1360–77.
39 McKay RG, Miller MJ, Ferguson JJ, *et al.* Assessment of left ventricular end-systolic pressure-volume relations with an impedance catheter and transient inferior vena cava occlusion: use of this system in the evaluation of the cardiotonic effects of dobutamine, milrinone, posicor and

epinephrine. *J Am Coll Cardiol* 1986;8:1152–60.

40 Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. *Circulation* 1986;73:586–95.

41 Burkhoff D. The conductance method of left ventricular volume estimation: methodologic limitation put into perspective. *Circulation* 1990;81:703–6.

42 Iwase M, Sotobata I, Yokota M, *et al*. Evaluation of pulsed Doppler echocardiography of the atrial contribution to left ventricular filling in patients with DDD pacemakers. *Am J Cardiol* 1986;58:104–9.

43 Nitsch J, Seiderer M, Bull U, Luderitz B. Evaluation of left ventricular performance by radionuclide ventriculography in patients with atrioventricular versus ventricular demand pacemakers. *Am Heart J* 1984;107:906–11.

44 Videen JS, Huang SK, Bazgan ID, Mechling E, Patton DD. Hemodynamic comparison of ventricular pacing, atrioventricular sequential pacing, and atrial synchronous ventricular pacing using radionuclide ventriculography. *Am J Cardiol* 1986;57:1305–8.

45 Masuyama T, Kodama K, Nakatani S, Kitabatake A. Effects of atrioventricular interval on left ventricular diastolic filling assessed with pulsed Doppler echocardiography. *Cardiovasc Res* 1989;23:1034–42.

46 Wish M, Fletcher RD, Gottdiener JS, Cohen AI. Importance of left atrial timing in the programming of dual-chamber pacemakers. *Am J Cardiol* 1987;60:566–71.

47 Naito M, Dreifus LS, David D, Michelson EL, Mardelli TJ, Kmetzo JJ. Reevaluation of the role of atrial systole to cardiac hemodynamics: evidence for pulmonary venous regurgitation during abnormal atrioventricular sequencing. *Am Heart J* 1983;105:295–302.

48 Faerestrand S, Oie B, Ohm O. Noninvasive assessment by Doppler and M-mode echocardiography of hemodynamic responses to temporary pacing and to ventriculoatrial conduction. *PACE* 1987;10:871–85.

49 Pepine CJ, Nichols WW, Conti CR. Aortic input impedance in heart failure. *Circulation* 1978;58:460–5.

50 Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation* 1980;62:105–16.

51 Burkhoff D, Alexander J Jr, Schipke J. Assessment of Windkessel as a model of aortic input impedance. *Am J Physiol* 1988;255:H742–53.

52 Sunagawa K, Maughan WL, Sagawa K. Stroke volume effect of changing arterial input impedance over selected frequency ranges. *Am J Physiol* 1985;248:H477–84.

53 Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. *Ann Biomed Eng* 1984;12:163–89.

54 Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;116:16–22.

55 Alpert MA, Curtis JJ, Sanfelippo JF, *et al*. Comparative survival following permanent ventricular and dual-chamber pacing for patients with chronic symptomatic sinus node dysfunction with and without congestive heart failure. *Am Heart J* 1987;113:958–65.

56 Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. *Am J Physiol* 1986;250:R1021–7.

57 Bedotto JB, Grayburn PA, Black WH, *et al*. Alterations in left ventricular relaxation during atrioventricular pacing in humans. *J Am Coll Cardiol* 1990;15:658–64.

58 Zile MR, Blaustein AS, Shimizu G, Gaasch WH. Right ventricular pacing reduces the rate of left ventricular relaxation and filling. *J Am Coll Cardiol* 1987;10:702–9.

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Changes in myocardial echo amplitude during reversible ischaemia in humans

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Abstract

Objective—**This study investigated the changes in regional myocardial ultrasonic backscatter, measured as myocardial echo amplitude, that occur during reversible myocardial ischaemia in humans.**

Design—**Left anterior descending coronary angioplasty was used to produce reversible myocardial ischaemia in human subjects. Regional myocardial echo amplitude was studied in the interventricular septum and left ventricular posterior free wall before, during, and after coronary occlusion with the angioplasty balloon. Wall motion analysis of the left ventricle was performed from simultaneous cross sectional echocardiographic imaging. Patients were studied prospectively.**

Patients—**Six patients (mean age 56 (SD 11), range 46 to 69 years) with single vessel, left anterior descending coronary artery stenoses, were investigated during elective coronary angioplasty. A total of 11 balloon inflations were studied.**

Setting—**All patient studies were performed at Harefield Hospital. Echo amplitude analysis was performed at the Royal Brompton Hospital.**

Interventions—**Angioplasty was performed by the usual procedure at Harefield Hospital for elective coronary angioplasty. All routine medication including β blockers and calcium antagonists were continued. Inflation pressures were up to 12 atm (1212 kPa) and mean inflation time ranged from 30 to 120 (86 (31)) s. In four studies the first inflation was examined, in three the second, in two the third, and in one each the fourth and fifth inflations. Echo amplitude and cross sectional echocardiographic studies were recorded with a 3·5 MHz Advanced Technology Laboratories (ATL) (720A/8736 series) mechanical sector scanner and an ATL Mark III (860–1 series) echocardiograph system with 45 dB logarithmic grey scale compression.**

Main outcome measures—**Regional echo amplitude was examined in four regions of the left ventricle—namely, the basal and mid-septum, and basal and mid-posterior wall. Consecutive end diastolic and end systolic frames were analysed and cyclic variation was determined as the difference between the level of echo amplitude at end diastole and at end systole. Measurements were made before balloon inflation, at peak inflation, and after balloon deflation. Regional wall motion and systolic wall thickening were analysed qualitatively.**

Results—**Before balloon inflation, cyclic variation in echo amplitude was noted in all regions (basal septum, 2·4 (SD 1·1) dB; mid-septum, 2·5 (1·1) dB; basal posterior wall, 3·3 (2·1) dB; mid-posterior wall, 3·9 (1·6) dB). During balloon inflation there was a significant fall in cyclic variation to 0·4 (0·9) dB ($p < 0{\cdot}0002$) in the mid-septum. This was predominantly owing to an increase in end systolic echo amplitude from 5·4 (2·0) dB to 9·3 (1·9) dB ($p \leqslant 0{\cdot}01$). This was associated with the development of severe hypokinesis or akinesis in the mid-septum. No significant changes in echo amplitude occurred in the three other regions examined. Changes were completely reversed after balloon deflation.**

Conclusions—**These results suggest a causal relation between occlusion of the supplying coronary artery and blunting of myocardial echo amplitude cyclic variation. It is suggested that balloon occlusion produced myocardial ischaemia. The resultant impairment of myocardial contraction then caused a blunting of cyclic variation in echo amplitude. The results of this study provide further data about the ability of quantitative studies of ultrasonic backscatter to identify alterations in the myocardium during injury.**

A link between cyclic variation in echo amplitude and cardiac contraction has been shown.[1] To assess this relation further a human model of reversible myocardial ischaemia was used to examine the effect of a reversible perturbation of cardiac contraction on cyclic variation of echo amplitude. Percutaneous transluminal coronary angioplasty of the left anterior descending artery provided an ideal model for studying left ventricular performance and function during short, controlled, and reversible episodes of myocardial ischaemia. Catheter balloon inflation performed during coronary angioplasty produces virtually total interruption of regional coronary blood flow. Numerous studies during coronary angioplasty have

Table 1 Coronary angioplasty patient characteristics

Patient	*Sex*	*Age*	*Total number of inflations studied*
1	M	46	1
2	M	47	1
3	F	69	2
4	M	50	2
5	F	54	3
6	M	69	2

shown the effect of balloon occlusion on global and regional left ventricular function using either M mode[2] or cross sectional echocardiography,[3-5] direct cine left ventriculography,[6-8] and intravenous digital subtraction ventriculography.[9] Similarly left ventricular filling dynamics have been studied during coronary angioplasty with high fidelity manometer tipped catheters[8] and Doppler echocardiography.[10] These studies suggested that coronary angioplasty provided an ideal model in which to study the effect of reversible myocardial ischaemia on cyclic variation in echo amplitude. As left anterior descending coronary artery angioplasty had been shown to produce changes in segmental shortening in the distal and mid-intraventricular septum,[5] cyclic variation in echo amplitude was examined in this region of the myocardium in a series of patients with single vessel left anterior descending stenoses who were undergoing coronary angioplasty.

Patients and methods

PATIENTS

Six patients with single vessel left anterior descending coronary artery disease, defined as greater than 70% luminal stenosis, were investigated during elective coronary angioplasty. No patient had a history of transmural myocardial infarction. Two patients were women and patient age ranged from 46 to 69 years (mean (SD) 56 (11) years). All patients previously had diagnostic coronary angiography and cine left ventriculography in the 30° right anterior oblique projection performed for the investigation of angina. In all cases left ventriculography was normal or showed minimal anterior hypokinesia only. A total of 11 balloon inflations were studied in the six patients; three inflations in one, two inflations in three, and one inflation each in the remaining two. The study was approved by the hospital ethical committee and all patients gave informed consent. Care was taken not to interfere with or prolong the therapeutic procedure. Table 1 shows characteristics of the patients.

Table 2 Characteristics of angioplasty balloon inflation, electrocardiographic changes, and pain

Patient No	*Inflation studied*	*Duration of inflation (s)*	*ST segment change*	*Cardiac pain*
1	1	90	No	No
2	1	40	Yes	Yes
3	1	30	Yes	Yes
3	2	90	Yes	Yes
4	2	60	Yes	No
4	4	120	Yes	No
5	1	90	No	No
5	3	100	No	No
5	5	120	No	No
6	2	90	No	No
6	3	120	No	No

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY PROTOCOL

Angioplasty was performed by the usual procedure for elective coronary angioplasty at Harefield Hospital. Patients were premedicated with intramuscular papavertetum and metoclopramide. All routine medication including β blockers and calcium antagonists was continued.

The angioplasty procedure was performed via the femoral approach. An intravenous single dose of 5000 units of heparin was administered at the start of the procedure. Non-ionic contrast medium, steerable guide wires, and balloon catheters with diameters varying from 2·5 to 3·5 mm were used. Inflation pressures were up to 12 atmospheres (1212 kPa) and mean inflation time (86 (SD 31)) ranged from 30 to 120 s. Table 2 shows that in four studies the first inflation was examined, in three the second, in two the third, and in one each the fourth and fifth inflations.

Continuous electrocardiographic monitoring was performed throughout the procedure with the six limb and augmented limb leads (I, II, III, aVL, aVF, and aVR) being monitored by a 7 series Seimens Elema Mingograf. The electrocardiogram was recorded immediately before and throughout each balloon inflation and after balloon deflation until any changes had resolved.

ECHO AMPLITUDE AND CROSS SECTIONAL ECHOCARDIOGRAPHY STUDIES

Echo amplitude and cross sectional echocardiographic studies were recorded with a 3·5 MHz Advanced Technology Laboratories (ATL) (720A/8736 series) mechanical sector scanner and an ATL Mark III (860-1 series) echocardiograph system with 45 dB logarithmic grey scale compression. To obtain the least modified echo amplitude signal, self correcting circuits were inactivated to avoid further differentiation of the original echo signal. Images were simultaneously displayed in grey scale and in colour by a Brompton Encoder (Alltek Hospital Supplies, Shepperton, Middlesex, UK) as they were recorded. On the colour scale each level of echo amplitude was represented as a single colour in the sequence: cyan, green, yellow, red, magenta, blue, and white, the last corresponding to maximum amplitude. The brightness of the displayed signal was modulated so that within each colour level, the luminosity was varied. This approach allowed a continuous range of echo amplitude to be displayed, and also meant that regions of low echo amplitude appeared with low brightness on the screen. These were less conspicuous on the final image and thus preserved the original amplitude perspective.[11]

All images were acquired with a standardised protocol to enable intrapatient and interpatient comparisons. Patients were studied in the supine position and long axis parasternal views were recorded. Gain settings were standardised: the master gain was increased until the parietal pericardium posterior to the left ventricle was just displayed at the highest level of the encoder (white). The depth compensation was then set to a linear ramp across the image at a rate of roughly 2 dB/cm. The gain settings were not altered thereafter. Images were stored on U-matic 3/4 inch video tape in a Sony VO 5800PS recorder.

Image analysis was performed by a Tandon PCA desk top computer. Stop frame end diastolic and end systolic images for analysis were selected by a video recorder with digital frame advance (Sony VO 5800PS). These frames were transferred from tape to a 512 × 256 × 6 bit frame store. Images were processed with an adaptive filtering process for the reduction of speckle as this decreased echo amplitude variance and allowed smaller sample sizes to be used.[12,13] Four areas of interest were defined, in the interventricular septum (basal and mid-septum), and posterior wall (basal and mid-posterior wall) as defined by the left ventricular anatomical nomenclature of Edwards *et al*[14] and measurements of 256 individual picture elements (pixels) were made from each area. Four separate measurements, each of 64 pixels, were made and averaged rather than one individual measurement of 256 pixels as this allowed the pixel matrix to be placed within the mid-myocardium and thus avoided including specular echoes from the endocardium or epicardium. A maximum pixel intensity for each image was derived by measuring the maximum colour intensity of the superimposed colour scale (usually corresponding to 52 levels of grey scale). This corresponded to a value of 45 dB and allowed echo amplitude values (dB) to be assigned (a grey scale level thus corresponding to approximately 0·86 dB). Individual pixel amplitudes were displayed as a histogram and a separate digital readout displayed mean, median, and SD values for each region measured. The display of the frequency histogram on the image proved useful, as an obviously bimodal form usually meant that specular echoes had mistakenly been included in the area of interest. Consecutive end diastolic and end systolic frames were analysed and cyclic variation determined as the difference between the level of echo amplitude at end diastole and at end systole. Cyclic variation index was calculated as the ratio: cyclic variation (end diastolic echo amplitude minus end systolic echo amplitude): end diastolic echo amplitude.

Table 3 Mean end diastolic and end systolic echo amplitude values during percutaneous transluminary coronary angioplasty (mean (SD))

	Pre-inflation	*Peak inflation*	*Post-inflation*
Basal septum:			
ED (dB)	7·5 (1·9)	7·8 (1·4)	7·0 (1·3)
ES (dB)	5·1 (1·2)	5·9 (1·6)	4·6 (0·8)
Mid-septum:			
ED (dB)	8·4 (2·2)	9·7 (2·1)	7·9 (2·1)
ES (dB)	5·9 (2·0)	9·3 (1·9)*	5·4 (1·2)
Basal PW:			
ED (dB)	8·1 (2·4)	7·9 (1·7)	7·2 (1·7)
ES (dB)	4·7 (1·0)	5·0 (0·8)	4·2 (0·9)
Mid-PW:			
ED (dB)	9·1 (2·0)	8·5 (2·3)	8·1 (2·0)
ES (dB)	5·2 (0·9)	5·6 (1·5)	4·6 (1·2)

*$p \leq 0{\cdot}0001$ (ANOVA) for all four groups, $p < 0{\cdot}005$ for all paired groups (Bonferroni's) comparing the mid-septum to other regions. Basal PW, basal posterior wall; ED, end diastole; ES, end systole; Mid-PW, mid-posterior wall.

Images for analysis were recorded at baseline with the deflated balloon and guide wire across the coronary lesion, at the peak of balloon inflation and after balloon deflation. In order not to interfere with the therapeutic procedure and patient safety and welfare, the timing of the imaging after deflation was by necessity variable. Seven balloon inflation images were acquired 15–30 seconds after deflation, but in the remaining four inflations, images could not be acquired until five, 10, 20, and 60 minutes after balloon deflation. In one study images of the mid-posterior wall were not suitable for analysis.

Regional wall motion analysis was performed qualitatively. Normal left ventricular wall motion was assessed by the amount of systolic myocardial thickening and inward endocardial motion. Abnormalities of segmental wall function were identified by a reduction in wall thickening and motion.

Results

CLINICAL OUTCOME, CHEST PAIN, AND ST SEGMENT CHANGES

All six patients underwent successful dilatation of their coronary stenoses. Significant ST segment shifts on the monitored electrocardiographic leads occurred during five balloon inflations. This was accompanied by chest pain consistent with cardiac ischaemia during three inflations (table 2). On all occasions ST segment changes and chest pain resolved rapidly after balloon deflation.

WALL MOTION AND THICKENING ABNORMALITIES

Before balloon inflation no significant wall motion abnormalities were present. During each of the 11 balloon inflations, severe hypokinesis or akinesis developed in the mid-septum and distal septum accompanied by diminished or absent wall thickening. Obvious hyperkinesis or severe hypokinesis of the ventricular wall was not seen elsewhere in the myocardium during any balloon inflation, except in the distal mid-posterior wall of two patients (patients 1 and 2). In the seven inflations where imaging was obtained for the first 30 seconds after balloon deflation the hypokinesis or akinesis seen resolved within the 30 s after deflation. For the remaining four inflations, resolution of the wall motion abnormalities was noted at the time of imaging after deflation.

END DIASTOLIC AND END SYSTOLIC REGIONAL ECHO AMPLITUDE

Table 3 shows mean values for regional echo amplitude for all four regions of ventricular myocardium at both end diastole and end systole. Tables 4–7 show the individual values for all patients. Values were greatest at end

Table 4 Individual echo amplitude (dB) at the basal septum for end diastole (ED) and end systole (ES) during angioplasty

Patient	*Variable*	*Inflation studied n*	*Pre-inflation*	*Peak inflation*	*Post-inflation*
1	ED	1	6·2	8·8	6·3
	ES		3·4	7·1	4·7
	CVI		0·45	0·20	0·25
2	ED	1	5·8	5·9	6·8
	ES		4·6	4·0	4·4
	CVI		0·20	0·32	0·35
3	ED	1	9·3	10·5	6·3
	ES		6·1	8·7	5·2
	CVI		0·35	0·17	0·17
3	ED	2	8·4	7·6	8·7
	ES		5·4	5·3	4·4
	CVI		0·36	0·30	0·50
4	ED	2	5·2	6·1	5·9
	ES		3·2	5·4	3·6
	CVI		0·37	0·11	0·39
4	ED	4	5·4	8·0	4·8
	ES		4·1	7·6	3·8
	CVI		0·24	0·05	0·20
5	ED	1	11·6	9·0	7·9
	ES		7·0	6·4	3·8
	CVI		0·39	0·29	0·52
5	ED	3	8·6	8·1	9·0
	ES		5·8	5·7	6·2
	CVI		0·32	0·30	0·31
	ED	5	7·9	7·7	7·4
	ES		6·4	6·5	5·3
	CVI		0·20	0·15	0·28
6	ED	2	6·7	6·0	7·3
	ES		5·3	4·3	4·8
	CVI		0·21	0·29	0·34
6	ED	3	7·6	7·7	6·7
	ES		4·6	3·4	4·3
	CVI		0·40	0·55	0·35

CVI, cyclic variation index.

diastole, and least at end systole. There was no significant difference between pre-inflation or post-inflation values at end diastole or end systole for the four regions. End systolic values in the mid-septum at peak inflation, however, were significantly greater ($p < 0\cdot005$) than values for the other three regions of myocardium examined. For the mid-septal region, systolic values of echo amplitude were greatly increased by peak inflation compared with pre-inflation ($p < 0\cdot01$) After balloon deflation, values fell significantly ($p < 0\cdot01$) and returned to values not significantly different from pre-inflation values.

Table 5 Individual echo amplitude (dB) at the mid-septum for end diastole (ED) and end systole (ES) during angioplasty

Patient	*Variable*	*Inflation studied n*	*Pre-inflation*	*Peak inflation*	*Post-inflation*
1	ED	1	7·8	9·8	6·5
	ES		4·0	9·4	5·7
	CVI		0·49	0·04	0·11
2	ED	1	7·2	8·8	5·9
	ES		5·6	9·0	3·7
	CVI		0·22	−0·03	0·37
3	ED	1	11·8	10·9	10·2
	ES		8·6	8·7	6·1
	CVI		0·27	0·20	0·41
3	ED	2	9·5	11·4	9·8
	ES		5·7	11·0	5·9
	CVI		0·39	0·04	0·40
4	ED	2	5·0	5·6	5·3
	ES		3·3	6·1	3·4
	CVI		0·33	−0·09	0·35
4	ED	4	5·3	7·2	5·1
	ES		4·1	7·4	4·0
	CVI		0·23	−0·03	0·21
5	ED	1	9·5	11·3	9·0
	ES		6·9	11·4	6·2
	CVI		0·27	−0·02	0·31
5	ED	3	9·6	9·8	10·6
	ES		7·7	10·5	6·9
	CVI		0·20	−0·07	0·35
5	ED	5	11·2	13·0	9·9
	ES		9·4	12·4	6·6
	CVI		0·16	0·05	0·34
6	ED	2	7·2	10·0	7·0
	ES		5·5	9·4	5·7
	CVI		0·24	0·07	0·19
6	ED	3	9·0	8·9	8·0
	ES		4·3	7·5	5·2
	CVI		0·52	0·16	0·35

CVI, cyclic variation index.

CYCLIC VARIATION IN ECHO AMPLITUDE

Table 8 shows mean values for cyclic variation. Tables 4–7 shows individual values for cyclic variation index. Values for pre-inflation and post-inflation were not significantly different for the four regions for either the absolute value of cyclic variation of echo amplitude (end diastolic echo amplitude minus end systolic echo amplitude) or the cyclic variation index. At peak inflation there was a significant fall in both these variables in the region of the mid-septum (ANOVA, $p \leqslant 0\cdot0001$) compared with both pre-inflation (Bonferroni's (comparison of pairs), $p \leqslant 0\cdot0002$ and $p \leqslant 0\cdot01$ respectively) and post inflation (Bonferroni's, $p \leqslant 0\cdot0002$ and $p \leqslant 0\cdot01$) values. This major decrease in cyclic variation was not seen in the other three regions of myocardium examined (figure).

SUMMARY OF RESULTS

During balloon inflation the mid-septum and distal septum of the ventricle became severely hypokinetic or akinetic. These changes were accompanied by significant changes in echo amplitude in the mid-septum. In this region a noticeable increase in end systolic echo amplitude occurred resulting in a fall in cyclic variation in echo amplitude to 16% of pre-inflation values and a similar fall in cyclic variation index to 10% of pre-inflation values. These changes paralleled the decrease in wall thickening seen qualitatively. After balloon deflation these changes reverted to pre-inflation values as did wall thickening.

Discussion

This study documents the effects of reversible coronary artery occlusion on cyclic variation of myocardial echo amplitude. In the mid-septal region of the left ventricular myocardium, after balloon occlusion of the supplying left anterior descending coronary artery, regional cyclic variation in echo amplitude was much blunted, falling to values less than 16% of pre-occlusion values. Cyclic variation index, which relates the level of cyclic variation to end diastolic levels of echo amplitude, also declined significantly to less than 10% of pre-occlusion values. These changes were completely reversible after balloon deflation suggesting a causal relation between occlusion of the supplying vessel and the blunting of cyclic variation. It is postulated that balloon coronary artery occlusion produced myocardial ischaemia in the territory of the left anterior descending coronary artery. The resultant impairment of myocardial contraction subsequently caused a blunting of cardiac cycle dependent variation in backscattered ultrasound. After balloon deflation and reperfusion these changes were rapidly reversed with no permanent sequelae. The evidence for this postulate is discussed further.

Table 6 Individual echo amplitude (dB) at the basal posterior wall for end diastole (ED) and end systole (ES) during angioplasty

Patient	*Variable*	*Inflation studied n*	*Pre-inflation*	*Peak inflation*	*Post-inflation*
1	ED	1	7·2	7·6	6·7
	ES		4·2	6·5	4·6
	CVI		0·42	0·15	0·32
2	ED	1	7·2	8·5	6·0
	ES		4·6	4·4	4·1
	CVI		0·37	0·48	0·31
3	ED	1	6·6	6·8	7·9
	ES		5·1	4·7	3·6
	CVI		0·22	0·31	0·54
3	ED	2	6·9	7·0	6·9
	ES		4·2	4·5	3·6
	CVI		0·40	0·36	0·48
4	ED	2	5·0	5·7	4·7
	ES		3·6	3·9	3·2
	CVI		0·28	0·31	0·31
4	ED	4	5·8	5·8	4·5
	ES		3·9	4·0	3·3
	CVI		0·33	0·31	0·25
5	ED	1	11·7	11·4	9·0
	ES		7·1	5·0	4·6
	CVI		0·40	0·56	0·50
5	ED	3	10·7	9·1	9·3
	ES		5·1	5·4	4·3
	CVI		0·52	0·40	0·54
5	ED	5	11·8	10·0	8·8
	ES		4·0	5·7	6·0
	CVI		0·66	0·44	0·32
6	ED	2	6·9	7·1	7·4
	ES		5·7	5·7	5·6
	CVI		0·17	0·20	0·25
6	ED	3	8·4	8·2	8·7
	ES		4·1	5·2	3·6
	CVI		0·52	0·37	0·59

CVI, cyclic variation index.

EVIDENCE FOR MYOCARDIAL ISCHAEMIA

Clinical findings

An early manifestation of acute myocardial ischaemia is the development of ST segment change on the electrocardiogram. Such changes were noted during five of the 11 balloon occlusions in this study. Previous studies in which limb lead electrocardiograms only were monitored have shown similar findings. Hauser *et al* found ST segment shift in seven of 16 patients undergoing left anterior descending coronary angioplasty.[3] Visser *et al* found ST segment change in four of 15 patients undergoing coronary angioplasty (10 single vessel left anterior descending, four single vessel right coronary artery, and one double vessel right coronary artery and left anterior descending coronary artery).[4] The use of 12 lead electrocardiographic monitoring greatly increases the frequency of ST segment change noted. In a group of 32 patients with mixed single and multiple vessel disease of whom 17 had angioplasty of the left anterior descending coronary artery, Labovitz *et al* analysed electrocardiograms to find significant ST segment changes in 25 of 31.[10] Wohlgelernter *et al*[8] detected ST segment changes in 12 of 14 patients during angioplasty of the left anterior descending coronary artery and Norell *et al* in 33 of 52 patients.[9] The use of intracoronary electrograms, recorded via the tip of the angioplasty guide wire positioned distal to the coronary stenosis being treated, greatly increased the yield of ST segment changes.[15 16] In a study by Jain and Gettes ST segment change occurred in 33 of 35 patients undergoing left anterior descending coronary angioplasty but was simultaneously detected in only 13 patients by observation of surface leads II and V_5.[16] The absence of ST segment change in over half (six of 11) of the balloon occlusions examined in our study does not therefore exclude acute myocardial ischaemia during those occlusions. Similarly the occurrence of chest pain during only three of 11 balloon inflations was consistent with that previously reported. Hauser *et al*[3] reported chest pain in eight of 16 patients during left anterior descending coronary angioplasty, and Visser *et al*[4] in five of 15 patients although only 11 of these patients underwent left anterior descending coronary angioplasty, the remainder being right coronary artery lesions. The absence of chest pain would appear to correlate poorly with the absence of acute myocardial ischaemia, chest pain being the last manifestation of ischaemia.[3]

Table 7 Individual echo amplitude (dB) at the mid-posterior wall for end diastole (ED) and end systole (ES) during angioplasty

Patients	*Variable*	*Inflation studied n*	*Pre-inflation*	*Peak inflation*	*Post-inflation*
1	ED	1	7·5	6·0	6·2
	ES		4·2	6·2	4·0
	CVI		0·44	−0·04	0·35
2	ED	1	8·7	8·8	8·5
	ES		6·0	9·2	7·1
	CVI		0·33	−0·04	0·16
3	ED	1	8·9	7·6	8·8
	ES		5·5	4·9	5·8
	CVI		0·38	0·36	0·34
3	ED	2	8·2	7·0	7·5
	ES		4·6	4·5	4·4
	CVI		0·45	0·37	0·42
4	ED	2	*	*	*
	ES		*	*	*
	CVI		*	*	*
4	ED	4	6·2	5·6	4·1
	ES		4·7	4·5	4·4
	CVI		0·25	0·20	0·12
5	ED	1	12·3	12·5	11·5
	ES		6·9	6·2	4·8
	CVI		0·44	0·50	0·58
5	ED	3	11·2	9·8	9·0
	ES		5·7	6·4	3·6
	CVI		0·50	0·35	0·60
5	ED	5	10·3	9·9	8·6
	ES		5·0	5·9	3·9
	CVI		0·52	0·41	0·55
6	ED	2	7·4	6·7	7·6
	ES		5·2	5·2	5·4
	CVI		0·30	0·23	0·28
6	ED	3	10·4	10·7	9·3
	ES		4·1	3·7	3·8
	CVI		0·61	0·66	0·59

*Not analysable; CVI, cyclic variation index.

Wall motion and systolic wall thickening

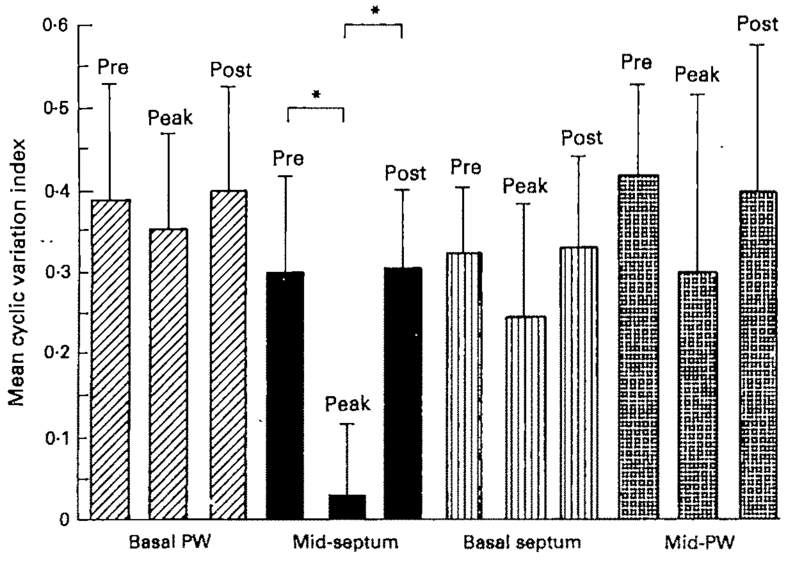
Coronary artery ligation in open chested dogs causes echocardiographically detectable systolic wall thinning in the ischaemic region within 30 s.[17 18] In our study, decreased systolic wall thickening was noted in the distal and mid-interventricular septum during all 11 balloon inflations studied. Similar findings have been well documented by other workers. Hauser *et al* found new or increased wall motion abnormalities in 14 of 16 patients during left anterior descending coronary angioplasty.[3] Hypokinesia was noted within 33 (19 (7)) s of balloon occlusion in all 14 patients and invariably preceded ST segment shift or chest pain where these occurred. Wall motion returned to normal within 30 seconds of balloon deflation in 12 of these patients. Alam *et al* studied eight patients with left anterior descending single vessel coronary artery disease during 14 balloon occlusions and noted a fall in systolic wall thickening of 50% or more in the interventricular septum during 13 of these occlusions.[2]

Table 8 Mean (SD) cyclic variation in echo amplitude and cyclic variation index during angioplasty

	Pre-inflation (dB)	*Peak inflation (dB)*	*Post inflation (dB)*	*p Value for all paired groups (Boniferoni)*
		Cyclic variation in echo ampitude		
Basal septum	2·4 (1·1)	1·9 (1·0)	2·4 (1·1)	p < 0·005
Mid-septum	2·5 (1·1)	0·4 (0·9)*	2·5 (1·2)	p < 0·005
Basal PW	3·3 (2·1)	2·9 (1·6)	3·0 (1·5)	p < 0·005
Mid-PW	3·9 (1·6)	2·8 (2·5)	3·5 (2·0)	p < 0·005
		Cyclic variation index		
Basal septum	0·32 (0·09)	0·25 (0·14)	0·33 (0·11)	p < 0·01
Mid-septum	0·30 (0·12)	0·03 (0·09)*	0·31 (0·10)	p < 0·01
Basal PW	0 39 (0·14)	0·35 (0·12)	0·40 (0·13)	p < 0·01
Mid-PW	0·42 (0·11)	0·30 (0·21)	0·40 (0·18)	p < 0·01

*p ≤ 0·0001 (ANOVA) for all four groups, comparing the mid-septum with other regions. Basal PW, basal posterior wall, Mid-PW, mid-posterior wall.

Wall thickening abnormalities began within 20 s. of balloon inflation in all 13 cases and returned to pre-occlusion levels within 20 s of balloon deflation. Visser *et al* documented similar wall motion abnormalities developing in 15 patients during 49 balloon inflations at a mean of 8 (3) s after balloon inflation.[4] Wall motion returned to baseline in all patients 19 (8) s after balloon deflation. Again Wohlgelernter *et al* reported 14 patients each undergoing angioplasty of an isolated left anterior descending stenosis who all developed severe hypokinesia (29%) or akinesia (71%) of the septal and apical region of the left ventricle by balloon inflation lasting 60 s.[5] Recovery to pre-occlusion values began within 15 (5) s (range 6 to 22) and was complete in all patients by 70 s after inflation with a mean time to full recovery of 43 (17) s. Evidence that ischaemia is the cause of the wall motion abnormalities recorded echocardiographically was provided by techniques to improve myocardial perfusion distal to the occluding angioplasty balloon. Timmis *et al* infused arterial blood through the angioplasty catheter into the distal coronary artery in 10 patients during 60 s balloon occlusions.[19] These inflations were compared with control occlusions with either no distal infusion or distal infusion with Hartman's solution. All dilatations without blood infusion in the 10 patients produced regional wall motion abnormalities within 16·0 (3·2) s. By contrast only one dilatation with distal blood infusion produced wall motion abnormalities. Infusion with Hartman's was not helpful in limiting wall motion abnormalities suggesting that oxygen delivery via arterial blood, rather than wash out of metabolites, was responsible for the benefit. Jaffe *et al* studied 42 patients undergoing coronary angioplasty using distal transcatheter coronary perfusion with oxygenated Fluosol DA (20% emulsion), a perfluorocarbon oxygen transport fluid.[20] They found a dramatic fall in left ventricular regional wall motion abnormality during perfusion with oxygenated Fluosol DA compared with controls. It seems that the development of regional wall motion abnormalities during coronary angioplasty not only reflects myocardial ischaemia but is also a sensitive and early marker of it. The development of regional wall motion abnormalities during coronary angioplasty in this study seem to reflect underlying myocardial ischaemia in the territory supplied by the left anterior descending coronary artery.



*Mean (SD) cyclic variation index during coronary angioplasty. During balloon inflation in the left anterior descending artery there was a significant fall in echo amplitude cyclic variation index in the mid-septal region only. After balloon deflation and the return of systolic myocardial thickening, cyclic variation index was restored to pre-inflation values. *p, ≤0·01; PW, posterior wall.*

CYCLIC VARIATION IN REGIONAL BACKSCATTERED ULTRASOUND

In 1983 and 1984, Madaras *et al* and Barzilai *et al* first reported cyclic variation in backscattered myocardial ultrasound.[21 22] They analysed myocardial integrated backscatter as a measure of backscattered ultrasound and examined this in a dog model after occlusion of the left anterior descending artery. Cyclic variation in integrated backscatter was significantly blunted in ischaemic areas of myocardium. These areas were previously delineated at open thoracotomy during brief coronary occlusion. The effects of reperfusion were not studied in this model. In a later study using a similar open chest dog model, cyclic variation in integrated backscatter was examined 10 min after coronary occlusion and after two hours of reperfusion. Cyclic variation at the left ventricular apex in the four dogs studied was 5·6 (1·4) dB at baseline and fell to 0·4 (1·5) dB after 10 min of occlusion (p < 0·02). After two hours of reperfusion, values were not significantly different from baseline at 3·9 (1·2) dB. Cross sectional echocardiographic apical four chamber views of the apex showed dyskinesis and loss of systolic thickening after 10 min of occlusion. This was substantially but not completely restored to baseline values after two hours of reperfusion. Corresponding values for systolic wall thickening at the apex were; baseline, 63·4 (17·7)%; 10 min occlusion, 2·2 (11·5)% (p < 0·001); two hours reperfusion, 52·9 (26·8)% (NS). Similar effects of ischaemia on cyclic variation of backscattered ultrasound from dog myocardium after coronary artery occlusion have been found by several other workers.[23–25]

Cyclic variation in backscattered myocardial ultrasound has also been found in humans.

This has been shown by integrated backscatter,[26-29] grey scale echo amplitude,[30] and colour encoded echo amplitude.[1] The effect of ischaemia on cyclic variation in backscattered ultrasound in humans is limited. Milunski *et al* studied 21 patients in a cardiac care unit within the first 24 hours after the onset of symptoms suggestive of acute myocardial infarction.[28] Areas of ischaemic injury were identified by cross sectional echocardiography and electrocardiography. Cyclic variation of integrated backscatter was measured in these areas and normal control areas of myocardium. Thrombolytic therapy was given to 17 patients. Cyclic variation in normal regions was 4·8 (0·5) dB compared with 0·8 (0·3) dB ($p < 0·05$) in regions with infarction. In the 15 patients who were serially studied and also underwent coronary angiography to define vessel patency, 10 had patent infarct related coronary arteries. In these patients the magnitude of cyclic variation increased with time (1·3 (0·6) dB to 2·5 (0·5) dB, $p < 0·05$) where in those with occluded infarct related vessels no significant recovery was seen (0·3 (0·3) dB to 0·6 (0·3) dB, NS). It was concluded that the restoration of cyclic variation in the patent vessel group represented the beneficial effect of reperfusion. Significantly the improvement in cyclic variation shown in this group was not accompanied by a noticeable improvement in wall motion.

It is probably incorrect, however, to compare the brief periods of coronary occlusion during clinical angioplasty with the prolonged periods of coronary occlusion in the study of Milunski *et al*,[28] and the animal studies already mentioned in which coronary occlusion times greater than five min were used. Many investigators have shown that although partial recovery of myocardial contractile function after brief ischaemia occurs promptly, complete recovery may require longer periods of reperfusion.[31-33] With more prolonged periods of myocardial ischaemia (>5 min) it is likely that structural changes are occurring. Myofibril stretching after similar periods of ischaemia are well described[34] as are other ultrastructural changes.[35] Zhao *et al* found disruption of the collagen matrix of dog myocardium with accompanying persistent myocardial dysfunction, after 12 sequential five min occlusions of the left anterior descending coronary artery.[36] This was unaccompanied by irreversible cellular damage. Therefore it is not surprising that cyclic variation may not be fully restored after several hours of reperfusion if ischaemia is prolonged more than a few minutes with resultant damage to cellular and extracellular structures. This contrasts with the rapid recovery of both myocardial systolic function and cyclic variation in echo amplitude that occurred with coronary reperfusion, after balloon deflation during angioplasty, which this study documents.

One other study, by Hajduczki *et al*[37] has documented changes in backscattered ultrasound during coronary angioplasty in humans. They examined patients during left anterior descending coronary angioplasty and showed a substantial change in cyclic variation of backscatter during balloon inflation. Backscatter fell from 8·6 (3·3) units pre-inflation to 3·2 (1·7) units at peak inflation ($p < 0·001$). They did not comment on whether this reversed after balloon deflation. They also noted an increase in cyclic variation of backscatter in areas of myocardium that were identified as hyperkinetic during balloon inflation. In our study the grouped data did not show a significant increase in cyclic variation of backscattered ultrasound in either basal segments of the left ventricle (where hyperkinesis would be most likely to occur) during balloon inflation, although increases in cyclic variation index of >10% were noted in both areas during two of the 11 inflations (tables 4, 6).

There are several explanations for the changes in cyclic variation that occur in association with myocardial ischaemia. Wickline *et al* have suggested a mechanism to explain cyclic variation in backscattered myocardial ultrasound (in their case integrated backscatter).[38] They suggested a relation between cyclic variation in integrated backscatter and myocardial contractile function which reflects cyclic alterations in myofibrillar elastic parameters, with the juxtaposition of intracellular and extracellular elastic elements that have different intrinsic acoustic impedances providing an appropriately sized scattering interface at the cellular level. Because acoustic impedance mismatch is partially determined by elastic modulus, changes in local elastic moduli which result from myocardial elastic elements not obeying Hook's law as they are stretched, may alter the degree of impedance mismatch. With a simple Maxwell type muscle model to depict cardiac cell mechanical behaviour, a model employing an extracellular parallel elastic element and intracellular series elastic and contractile elements can be constructed. This model predicts the decrease in backscattered ultrasound found during systole. Cardiac cycle dependent alterations in the degree of local acoustic impedance mismatch may therefore elicit concomitant changes in backscattered ultrasound. More recently Rijsterborgh *et al* confirmed in animal studies that the higher systolic backscatter seen during ischaemia could be explained by the decrease in wall thickness that occurs with ischaemia and not by the ischaemia itself, in keeping with the influence of myocardial contraction on cyclic variation.[39] Other possibilities include alterations in the relative insonifying angle due to changing fibre angle and shape during the cardiac cycle as it is known that both reflection and attenuation of ultrasound alter according to the direction of fibre insonification.[40] Whatever the exact basis of cyclic variation in backscattered ultrasound, there is no doubt an important relation with contractile events occuring within the myocardium at either a cellular or fibre level. As myocardial ischaemia occurs these contractile events are disrupted and cyclic variation as a result is blunted. Changes in myocardial blood flow during coronary occlusion must also be considered as a cause of the blunting of cyclic variation in backscattered ultrasound, as changes in red blood cell concentration have been shown to noticeably affect overall levels (as distinct from cyclic variation) of backscattered ultrasound in experimental models.[41–43] Wickline *et al*, however, in a series of experiments on perfused and non-perfused dog hearts that were cyclically distended and relaxed by an intracavitary ventricular balloon, showed that myocardial perfusion with whole blood did not contribute significantly to the phenomenon of cyclic variation in backscattered ultrasound.[38] Importantly, in this study there was an increase in end diastolic echo amplitude in the mid-septum during balloon inflation from 8·4 (2·2) dB to 9·7 (2·1) dB that is significant ($p < 0·05$) if the mid-septum alone is considered. This would be consistent with a fall in concentration of formed blood elements in the myocardium during coronary occlusion.[43]

Conclusion

It is likely that balloon coronary occlusion during angioplasty results in reversible myocardial ischaemia which produces a reversible blunting of cardiac cycle dependent backscattered ultrasound after temporary contractile dysfunction induced by ischaemia. The results of this study are consistent with this hypothesis and provide further data on the ability of techniques involved in the quantitative study of backscattered ultrasound to clarify alterations in the myocardium during injury.

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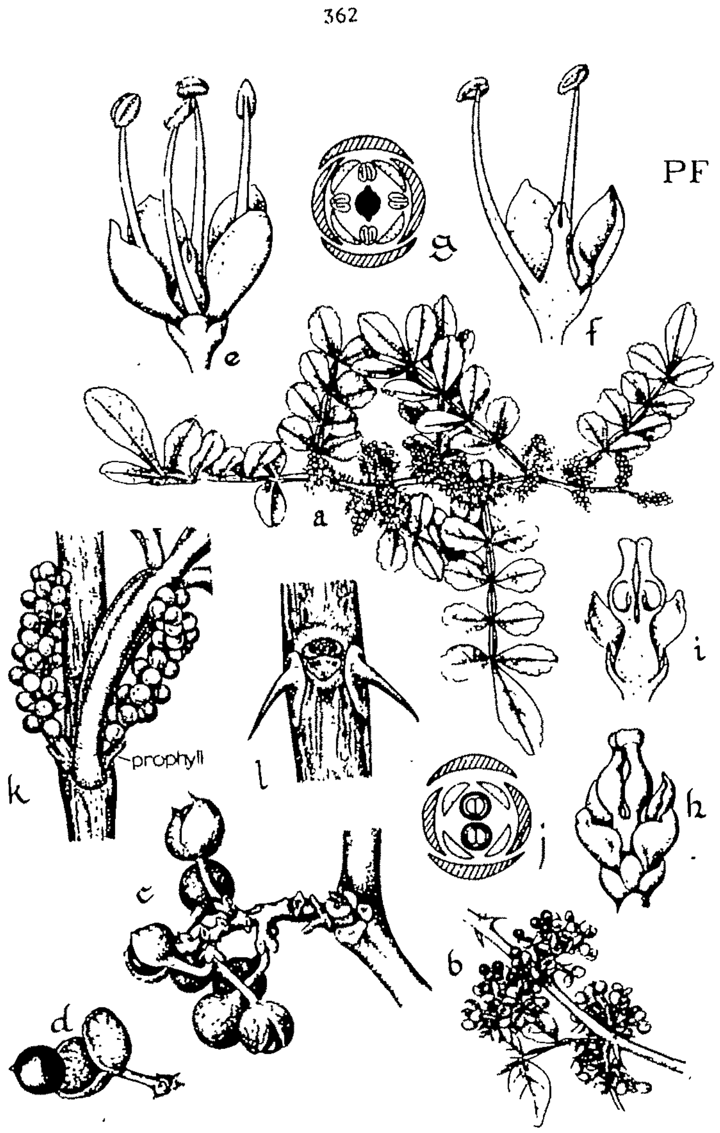
1 Lythall DA, Gibson DG, Ilsley CD, Yacoub MH. Changes in myocardial echo amplitude related to the cardiac cycle. *Eur Heart J* 1989;10(suppl):220.
2 Alam M, Khaja F, Brymer J, Marzelli M, Goldstein S. Echocardiographic evaluation of left ventricular function during coronary artery angioplasty. *Am J Cardiol* 1986; 57:20–5.
3 Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC, Dudlets P. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol* 1985;5:193–7.
4 Visser CA, David GK, Kan G, *et al.* Two-dimensional echocardiography during percutaneous transluminal coronary angioplasty. *Am Heart J* 1986;111:1035–41.
5 Wohlgelernter D, Cleman M, Highman HA, *et al.* Regional myocardial dysfunction during coronary angioplasty: evaluation by 2-dimensional echocardiography and 12 lead electrocardiography. *J Am Coll Cardiol* 1986;7: 1245–54.
6 Doorey AJ, Mehmel HC, Schwartz FX, Kubler W. Amelioration by nitroglycerine of left ventricular ischaemia induced by percutaneous transluminal coronary angioplasty: assessment by haemodynamic variables and left ventriculography. *J Am Coll Cardiol* 1985;6:267–74.
7 Serruys PW, Wijns W, Van Den Brand M, *et al.* Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:25–36.
8 Piscione F, Hugenholtz PG, Serruys PW. Impaired left ventricular filling dynamics during percutaneous transluminal angioplasty for coronary artery disease. *Am J Cardiol* 1987;59:29–37.
9 Norell MS, Lyons JP, Gershlick AH, *et al.* Assessment of left ventricular performance during percutaneous transluminal coronary angioplasty: a study by intravenous digital subtraction ventriculography. *Br Heart J* 1988; 59:419–28.
10 Labovitz AJ, Lewen MC, Kern M, Vandormael M, Deligonal U, Kennedy HL. Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischaemia produced by angioplasty. *J Am Coll Cardiol* 1987;10:748–55.
11 Logan-Sinclair RB, Wong CM, Gibson DG. Clinical application of amplitude processing of echocardiographic images. *Br Heart J* 1981;45:621–7.
12 Bamber JC, Daft C. Adaptive filtering for reduction of speckle in ultrasonic pulse-echo images. *Ultrasonics* 1986; (Jan):41–4.
13 Massey RJ, Logan-Sinclair RB, Bamber JC, Gibson DG. Quantitative effects of speckle reduction on cross sectional echocardiographic images. *Br Heart J* 1989;62:298–304.
14 Edwards WD, Tajik AJ, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. *Mayo Clin Proc* 1981;56:479–97.
15 Freidman PL, Shook TL, Kirschenbaum JM, Selwyn AP, Ganz P. Value of the intracoronary electrogram to monitor myocardial ischaemia during percutaneous transluminal coronary angioplasty. *Circulation* 1986;74:330–9.
16 Jain A, Gettes LS. Patterns of ST-segment change during acute no-flow myocardial ischaemia produced by balloon occlusion during angioplasty of the left anterior descending coronary artery. *Am J Cardiol* 1991;67:305–7.
17 Pandian NG, Kieso RA, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. II. Relationship between systolic wall thinning and regional myocardial perfusion in severe coronary stenosis. *Circulation* 1982;66:603–11.
18 Pandian NG, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. I. Sensitivity and specificity in detecting transient myocardial dyskinesis: comparison with sonomicrometers. *Circulation* 1982;66:597–602.
19 Timmis AD, Crick JCP, Griffin B, Sowton E. Prevention of regional myocardial ischaemia during PTCA—the effects of infusing arterial blood. *Br Heart J* 1989;61:628 (abstr).
20 Jaffe CC, Wohlgelernter D, Cabin H, *et al*. Preservation of left ventricular ejection fraction during percutaneous transluminal coronary angioplasty by distal transcatheter perfusion of oxygenated Fluosol DA 20%. *Am Heart J* 1988;115:1156–64.
21 Madaras EI, Barzilai B, Perez JE, Sobel BE, Miller JG. Changes in myocardial backscatter throughout the cardiac cycle. *Ultrasonic Imaging* 1983;5:229–39.
22 Barzilai B, Madaras EI, Sobel BE, Miller JG, Perez JE. Effects of myocardial contraction on ultrasonic backscatter before and after ischemia. *Am J Physiol* 1984;247:478–83.
23 Wickline SA, Thomas LJ III, Miller JG, Sobel BE, Perez JE. Sensitive detection of the effects of reperfusion on myocardium by ultrasonic tissue characterization with integrated backscatter. *Circulation* 1986;74:389–400.
24 Sagar KB, Rhyne TL, Warltier DC, Pelc L, Wann LS. Intramyocardial variability in integrated backscatter: effects of coronary occlusion and reperfusion. *Circulation* 1987;75:436–42.
25 Milunski MR, Mohr GA, Wear KA, Sobel BE, Miller JG, Wickline SA. Early identification with ultrasonic integrated backscatter of viable but stunned myocardium in dogs. *J Am Coll Cardiol* 1989;14:462–71.
26 Vered Z, Barzilai B, Mohr GA, *et al*. Quantitative ultrasonic tissue characterization with real-time integrated backscatter imaging in normal human subjects and in patients with dilated cardiomyopathy. *Circulation* 1987;5:1067–73.
27 Milunski MR, Canter CE, Wickline SA, Sobel BE, Miller JG, Perez JE. Cardiac cycle dependent variation of integrated backscatter is not distorted by abnormal myocardial wall motion in human subjects with paradoxical septal motion. *Ultrasound Med Biol* 1989;15:311–7.
28 Milunski MR, Mohr GA, Perez JE, *et al.* Ultrasonic tissue characterization with integrated backscatter: Acute myocardial ischaemia, reperfusion, and stunned myocardium in patients. *Circulation* 1989;80:491–503.
29 Masuyama T, Nellessen U, Schnittger I, Tye TL, Haskell WL, Popp RL. Ultrasonic tissue characterization with a real time integrated backscatter imaging system in normal and aging human hearts. *J Am Coll Cardiol* 1989;14: 1702–8.
30 Olshansky B, Collins SM, Skorton DJ, Prasad NV. Variation of left ventricular myocardial gray level on two-dimensional echocardiograms as a result of cardiac contraction. *Circulation* 1984;6:972–7.
31 Heyndrickx GR, Millar RW, McRitchie R, Maroko PR, Vatner S. Regional myocardial function and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. *J Clin Invest* 1975;56:978–85.
32 Kloner RA, DeBoer LWV, Darsee J, Ingwall JS, Braunwald D. Recovery from prolonged abnormalities, of canine myocardium salvaged from ischaemic necrosis by coronary reperfusion. *Proc Natl Acad Sci USA* 1981; 78:7152–6.
33 Weiner JM, Apstein CS, Arthur JH, Pirzada FA, Hood WB. Persistence of myocardial injury following brief periods of coronary occlusion. *Cardiovasc Res* 1976;10:678–86.
34 Jennings RB, Ganote CE. Structural changes in myocardium during acute ischaemia. *Circ Res* 1974;34/35 (suppl III):156–72.
35 Kloner RA, Ganote CE, Whalen DA, Jennings RB. Effect of a transient period of ischemia on myocardial cells. II. Fine structure during the first few minutes of reflow. *Am J Pathol* 1974;74:399–422.
36 Zhao M, Zhang H, Robinson TF, Factor SM, Sonnenblick EH, Eng C. Profound structural alterations of the extracellular collagen matrix in postischemic dysfunctional ("Stunned") but viable myocardium. *J Am Coll Cardiol* 1987;10:1322–34.
37 Hajduczki I, Jaffe M, Areeda J, *et al.* Ultrasonic backscatter and 2D echocardiographic wall motion during PTCA (abstract). *Circulation* 1988;78:(suppl II):442.

38 Wickline SA, Thomas LJ III, Miller JG, Sobel BE, Perez JE. A relationship between ultrasonic integrated backscatter and myocardial contractile function. *J Clin Invest* 1985;76:2151–60.
39 Rijsterborgh H, Mastik F, Lancée CT, Sassen LMA, Verdouw PD, Roelandt J, *et al*. The relative contributions of myocardial wall thickness and ischaemia to ultrasonic myocardial integrated backscatter during experimental ischaemia. *Ultrasound Med Biol* 1991;17:41–8.
40 Aygen M, Popp RL. Influence of the orientation of myocardial fibres on echocardiographic images. *Am J Cardiol* 1987;60:147–52.
41 Shung KK, Siegelmann RA, Reed JM. Scattering of ultrasound by blood. *IEEE Trans Biomed Eng* 1976; 23:460–7.
42 Shung KK, Reid JM. Ultrasonic scattering from tissues. *Proceedings of the IGEE Ultrasonics Symposium* 1977; 77(CH1264–ISU):230–3.
43 Mimbs JW, Bauwens D, Cohen RD, O'Donnell M, Miller JG, Sobel BE. Effects of myocardial ischemia on quantitative ultrasonic backscatter and identification of responsible determinants. *Circ Res* 1981;49:89–96.

PLANTS IN CARDIOLOGY



The Linnean Society

Zanthoxylum fagara
Tomlinson TB. *The biology of trees native to tropical Florida*. Allston: Harvard University Print Office, 1980:362.
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Fagarine

In 1932 G Stuckert was the first to isolate a new alkaloid, fagarine, from the Argentinian plant *Fagara coco* (Rutaceae); and with A Sartori he showed that it had a depressant action on the myocardium of rabbits. Further work at the University of Cordoba by Moisset de Espanés and others showed that fagarine raised the threshold for atrial and ventricular fibrillation in response to faradic stimulation, and that it decreased the incidence of ventricular fibrillation after coronary ligation in dogs. In all these experiments it was more effective than quinidine. Then A Taquini tried its effect in six patients with atrial flutter or fibrillation who were resistant to quinidine. In all of them intramuscular fagarine restored sinus rhythm within 30 minutes (*Science* 1945;**102**:69–70). In 1948 David Scherf showed that fagarine reliably reverted atrial fibrillation induced by aconitine in dogs (*Proceedings of the Society for Experimental Biology and Medicine* 1948;**67**: 59–60).

The genus *Fagara* has been merged with *Zanthoxylum* and the name of the original *F coco* (Gill.) Engl. is now *Z coco* Gill ex Hook and Arn. The illustration is of a closely related species. The South African plant *Z capensis*, a "fever tree". is used medicinally.

The family Rutaceae is widespread, especially in the tropics, and it includes *Pilocarpus microphyllus*, the source of pilocarpine. Citrus fruits belong to this family. Rutaceae is the fourth family of plants described in Plants in Cardiology with antiarrhythmic properties—quinidine, procaine, and lignocaine all being derived from other families. It would be interesting to know whether fagarine is still under investigation.

A HOLLMAN

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Symptomatic and silent myocardial ischaemia in hypertensive patients with left ventricular hypertrophy

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Abstract

Objective—To assess the prevalence of symptomatic and silent myocardial ischaemia in patients with hypertensive left ventricular hypertrophy.

Design—Cross sectional study.

Setting—University department of medical cardiology.

Patients—90 patients (68 men and 22 women; mean age 57 (range 25 to 79)) with left ventricular hypertrophy due to essential hypertension.

Interventions—48 hour ambulatory ST segment monitoring (all patients), exercise electrocardiography (n = 79), stress thallium scintigraphy (n = 80), coronary arteriography (n = 35).

Results—43 patients had at least one episode of ST segment depression on ambulatory electrocardiographic monitoring. The median number of episodes was 16 (range 1 to 84) with a median duration of 8·6 (range 2 to 17) min. Over 90% of these episodes were clinically silent. 26 patients had positive exercise electrocardiography and 48 patients had reversible thallium perfusion defects despite chest pain during exercise in only five patients. 18 of the 35 patients who had coronary arteriography had important coronary artery disease. Seven of these patients gave no history of chest pain.

Conclusions—Symptomatic and silent myocardial ischaemia are common in hypertensive patients with left ventricular hypertrophy, even in the absence of epicardial coronary artery disease.

There is now considerable epidemiological evidence that hypertensive patients with left ventricular hypertrophy are at increased risk of all manifestations of coronary heart disease.[1–3] Myocardial infarction and stable and unstable angina are all more common in these patients. This relation persists even after correction for the contribution of hypertension and other risk factors for atherosclerosis.[2 3] The presence of electrocardiographic left ventricular hypertrophy carries a prognosis similar to that of electrocardiographic evidence of a previous myocardial infarction.[3–5]

Despite the large number of epidemiological studies there are few data on the objective assessment of myocardial ischaemia in individual patients with hypertensive left ventricular hypertrophy. We have shown previously that patients with hypertensive left ventricular hypertrophy may have thallium perfusion abnormalities or coronary artery disease and yet be symptom free.[6] Because chest pain was an exclusion criterion for the previous study, however, the patients were not representative of all patients with hypertensive left ventricular hypertrophy. We therefore conducted the present study to assess prevalence of symptomatic and asymptomatic myocardial ischaemia in hypertensive patients with left ventricular hypertrophy attending a hospital based hypertension clinic and to determine the best non-invasive method to identify prognostically important coronary artery disease in these patients.

Patients and methods

We recruited 90 consecutive patients (68 men) (mean age 57 (range 25 to 79) years) who agreed to be in the study and fulfilled the following criteria:

(a) they had essential hypertension—secondary hypertension was excluded by clinical evaluation, routine biochemical screening, chest *x* ray, and, where indicated, intravenous pyelography.

(b) they had the electrocardiographic pattern of left ventricular hypertrophy and strain.

The study was approved by the ethics committee of Glasgow Royal Infirmary. The patients provided written informed consent for the invasive procedures and verbal consent for the non-invasive investigations.

ELECTROCARDIOGRAPHY

Twelve lead electrocardiograms were recorded with the Glasgow CARE (computer assisted reporting of electrocardiograms) system.[7] For the purposes of this study left ventricular hypertrophy and strain were defined as ST segment depression and T wave inversion of 0·1 mV or more in I, aVL, V5, or V6 in the presence of voltage criteria ($SV1 + RV5 > 3·5$ mV) for left ventricular hypertrophy.

ECHOCARDIOGRAPHY

We assessed the degree of left ventricular hypertrophy by echocardiography performed with an Advanced Technology Laboratories Ultramark 8 mechanical scanner with a 3 MHz transducer. Left ventricular mass was calculated by an anatomically validated method.[8]

EXERCISE ELECTROCARDIOGRAPHY

The patients exercised on a Tunturi bicycle ergometer. The workload was increased by 50 W every 3 minutes up to a symptom limited maximum. At the end of each stage and at maximum exercise blood pressure was measured by cuff sphygmomanometer, a simultaneous 12 lead electrocardiogram was recorded, and the heart rate was estimated from the RR interval. We calculated the maximal oxygen uptake from the maximum load during the final stage of exercise using nomograms from normal subjects[9] and patients with cardiovascular disease.[10] The double product was calculated from the product of systolic pressure at peak exercise and maximal heart rate.

The exercise electrocardiograms were recorded at a paper speed of 25 mm/s on a Siemens-Elema Mingocard 3. ST segment depression was defined as horizontal or down sloping ST segment depression of 0·1mV or greater at 80 ms after the J point.[11] In view of the high rate of electrocardiographic false positives in patients with resting ST-T wave changes[12] we only considered additional ST segment depression of 0·2 mV or more compared with the resting depression as significant in patients with left ventricular hypertrophy and strain.[13] The number of leads showing significant ST segment depression was also counted. In patients with abnormal resting electrocardiograms another method which may be useful is the measurement of changes in R wave amplitude during exercise.[12] The amplitudes of the R waves of five consecutive complexes at rest and peak exercise were therefore measured, with an abnormal R wave response defined as one in which there was no change or an increase in the amplitude with exercise.[14]

AMBULATORY ST SEGMENT MONITORING

Ambulatory electrocardiograms were recorded for 48 hours with a Medilog II FM recorder and analysed by an experienced technician using a computer assisted technique.[15] Two leads were recorded, CM5 on channel 1 and a V2 type lead on channel 2. The ST segment shifts were measured at 80 ms after the J point. Significant ST depression was defined as horizontal or downsloping ST depression of greater than 0·1 mV that persisted for more than one minute.[16] In our study, the resting ST-T wave changes of all patients (with left ventricular hypertrophy and strain) meant that channel 1 (CM5) would not appear abnormal under normal circumstances. Therefore the criteria were modified so that a positive result was recorded only if there was additional ST depression of more than 0·2 mV compared with the resting changes. In the system used, the computer analysis provides a minute by minute trend of the ST segment shifts and this was scanned manually for periods of ST segment depression fulfilling the criteria. An episode was counted only if ST segment depression was detected by review of these trends and confirmed on hardcopy printout. The total duration of ST segment depression was calculated to the nearest minute from the computer summary.

STRESS THALLIUM SCINTIGRAPHY

Thallium-201 chloride (80 MBq) was injected at peak exercise via an indwelling antecubital cannula 30 to 60 s before the end of symptom limited maximal exercise. Images were acquired in list mode for 300 s for each projection and electrocardiographically gated. Data were acquired in the anterior, 45° left anterior oblique and 75° left anterior oblique projections by a mobile gamma camera (General Electric) fitted with a high sensitivity collimator interfaced to a dedicated computer. The images were then put into an eight frames per cycle gated study format representative of the cardiac cycle. Beats deviating by 20% or more of the mean RR interval were excluded. Redistribution images were obtained four hours later in the same fashion.

The studies were analysed by visual inspection of the gated study by two experienced observers. The ventricle was divided into five segments in each projection. A perfusion defect was deemed to be present if the predominant colour in that segment was reduced by at least two of the 16 colour levels. A reversible perfusion defect was defined as one that showed partial or complete resolution on the redistribution images compared with the post-stress images.[17] Images that did not change significantly were classified as fixed defects.

REPRODUCIBILITY OF INTERPRETATION OF THALLIUM SCINTIGRAPHY

The intraobserver and interobserver variability was assessed for 50 of the thallium scans. The images were reviewed independently by two observers (SP and WM). Each observer completed a pre-printed report form representing the six images from each patient (three immediately after exercise and three redistribution images). After completion of the reports the number of regions in which there was a disagreement was compared firstly between the observers and secondly between the same observer on two different occasions.

In total there were 1500 regions in these 50 patients and a disagreement in perfusion was present in 33 regions between observers and in 37 between the first and second review of the same scan. Thus the interobserver reproducibility was 97·8% and intraobserver reproducibility was 97·5%.

CORONARY ARTERIOGRAPHY

We considered the desirability of coronary arteriography for each patient bearing in mind their age, general health, and coexistent medical problems. Sixty two patients were considered suitable and 35 agreed to undergo coronary arteriography. The remaining 27 patients declined mainly because of a reluctance to be admitted to hospital rather than anxiety about the procedure. There was no conscious bias towards recruiting patients with chest pain for coronary arteriography. Indeed the patients who did not have invasive investigations tended to be older and therefore might have been expected to have more coronary artery disease.

The femoral artery was cannulated by the

Table 1 Clinical characteristics of the patients

Age (y)	57 (range 25 to 79)	
Sex (men:women)	68:22	
Angina	21	
Previous MI	5	
SBP (mm Hg)	155	(28)
DBP (mm Hg)	89	(15)
Duration of HT (y)	7·4	(8·0)
LVMI (g/m^2)	196·4	(50·5)
Drug therapy:		
Thiazides (No (%))	34	(38)
β Blockers (No (%))	38	(42)
Ca antag (No (%))	40	(44)
ACE I (No (%))	23	(25)
Mean No of drugs	2·51	(1·4)

MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; LVMI, left ventricular mass index; Ca antag, calcium antagonists; ACE I, angiotensin converting enzyme inhibitors.
Results are expressed as mean (SD) unless otherwise stated.

Table 2 Exercise electrocardiography (n = 79)

Result	*n*	*No with chest pain*
Additional ST segment depression (>0·2 mV)	26	5
Increased number of leads showing ST segment depression	14	2
Abnormal R wave response	40	2
Two positive criteria	21	3
Three positive criteria	2	0
Exercise induced ventricular ectopic beats	12	0
Normalisation of ST segment depression	12	0
No exercise induced ECG changes	22	0

Seldinger technique under local anaesthetic and the coronary arteries were injected selectively. The films were analysed in detail by at least two observers. A vessel was defined as significantly diseased where luminal diameter was reduced by more than 50%.

STATISTICAL ANALYSIS[18]

To compare the two groups of data we used a two sample *t* test if the data were normally distributed and a non-parametric Mann-Whitney U test when the distribution was skewed. Differences in the frequency of discrete variables between groups were assessed by the χ^2 test with Yates' correction for small numbers where appropriate. For all analyses p < 0·05 was considered significant.

Results

Twenty one of the 90 patients gave a history of angina (New York Heart Association (NYHA) Grade I in five, grade II in 10, and grade III in six (table 1) and a further 12 had atypical chest pain. Five patients had had a previous myocardial infarction. Eighty eight had a calculated left ventricular mass index above the 97th percentile.

Table 3 Ambulatory ST segment monitoring

		Symptoms		
ST depression segment	*No of patients*	*Nil*	*Chest pain*	*Other**
Nil	47	41	1	5
Channel I	27	19	5	2
Channel II	9	6	1	2
Both channels	7	5	1	1

*Other symptoms recorded were arm pain (one), breathlessnes (six), and palpitations (three).

EXERCISE ELECTROCARDIOGRAPHY

Table 2 shows that of the 79 patients who underwent exercise electrocardiography 22 had no exercise induced electrocardiographic changes.

Positive exercise electrocardiography

Twenty six patients had ST segment depression of greater than 0·2 mV in addition to the depression at rest. Fourteen patients had an increased number of leads showing ST segment depression and the R wave response was abnormal in 40 patients. Twenty one patients fulfilled two of these criteria and two patients fulfilled all three.

Other electrocardiographic changes

Twelve patients had complete normalisation of their ST segments, 19 had a reduction in the number of leads showing ST segment depression, and 12 patients had exercise induced ventricular extrasystoles.

Relation to symptoms

The end point of exercise was chest pain in five patients, breathlessness in 11, leg fatigue in 42, and general fatigue in 21.

AMBULATORY ELECTROCARDIOGRAPHY

Table 3 shows that at the time of the monitoring period most patients had resting ST-T changes detectable on channel I. Only ST segment depression of greater than 0·2 mV in addition to the resting value was, therefore, considered significant. By contrast, no patients had a resting electrocardiogram that showed ST segment depression in channel II.

Forty three patients had at least one episode of ST segment depression (as defined above) during the monitoring period. This was detected on channel I in 27 patients, on channel II in nine patients, and on both channels in seven patients. The median number of episodes was 16 (range 1 to 84) with a median duration of 8·6 (range 2 to 17) min. Fourteen of the 27 patients with ST segment depression in channel I had accentuation of the resting ST segment depression. In the remaining 13 patients the pattern of ST segment depression changed.

Relation to symptoms

Eighteen patients recorded symptoms on the diary cards: chest pain was reported by eight, arm pain by one, breathlessness by six, and palpitation by three. In six of the patients who reported symptoms no abnormality was detected on ambulatory monitoring. Episodes of ST segment depression corresponded to symptoms in seven of the patients with chest pain, four with breathlessness, and one with palpitation. Over 90% of the episodes, however, were asymptomatic.

THALLIUM PERFUSION SCINTIGRAPHY

Perfusion defects

Small apical defects were present in 73 out of 80 patients and were presumably a reflection of the relative apical thinning[19] that is exaggerated in the presence of left ventricular hypertrophy. There were abnormalities of perfusion in

Table 4 Comparison of exercise haemodynamics and symptoms in patients with and without reversible thallium perfusion defects (mean (1 SD))

	Thallium perfusion defect			
	Present		Absent	
Number	48		32	
Exercise duration (min)	3·9	(1·7)	4·6	(2·2)
Peak heart rate (beats/min)	121	(23)	117	(28)
Peak systolic BP (mm Hg)	195	(31)	209	(30)
Double product (mm Hg × beats/min × 10^2)	238	(67)	248	(85)
Max predicted MVo$_2$ (%)	70	(26)	79	(29)
Chest pain (No)	5*		0	
Breathlessness (No)	8		3	

*p < 0·05. RPD, reversible perfusion defect; MVo$_2$, myocardial oxygen consumption.

Table 5 Comparison of major risk factors in patients with and without coronary artery disease (mean (1 SD))

	CAD (n = 18)		NCA (n = 17)	
Age (y)	58	(6·4)*	51	(8·9)
Smokers (No)	13		16	
Duration of HBP (y)	7·0	(5·2)	6·2	(8·9)
SBP (mm Hg)	158	(32)	154	(34)
DBP (mm Hg)	90	(16)	94	(20)
Total cholesterol (mmol/l)	6·5	(1·1)	5·9	(1·4)
LDL cholesterol (mmol/l)	4·4	(0·9)	3·7	(1·4)
HDL cholesterol (mmol/l)	1·2	(0·4)	1·3	(0·5)

*p < 0·05. CAD, coronary artery disease; NCA, normal coronary arteries.

regions other than the apex in 64 patients. These perfusion defects were fixed in 16 and reversible in 48 patients.

Relation to symptoms

Exercise capacity in general was poor. The end point of exercise in those with reversible perfusion defects was leg fatigue in 20, general fatigue in 15, breathlessness in eight, and chest pain in five patients. Table 4 shows that the exercise duration and haemodynamic function were similar in those with reversible perfusion defects and those without.

CORONARY ANGIOGRAPHY

Thirty five patients underwent coronary arteriography: 17 had normal coronary arteries and 18 had significant coronary artery disease. Of these, three had single, one had double, and 14 had triple vessel disease.

RELATION TO SYMPTOMS

Of the 18 patients with coronary artery disease seven gave no history of chest pain (five with triple vessel disease and two with single vessel disease). Eight had mild (NYHA I or II) angina and three had moderate (NYHA III) angina. Chest pain was also a complaint in five of the patients with normal coronary arteries, mild (NYHA II) in four, and moderate (NYHA III) in one. A complaint of breathlessness was equally common in the two groups (10 of those with coronary artery disease and eight of those with normal coronary arteries).

COMPARISON OF PATIENTS WITH AND WITHOUT CORONARY ARTERY DISEASE

Table 5 shows that the patients with coronary artery disease were older (mean (SD) 58 (6·4) *v* 51 (8·9) years, 95% confidence interval 1 to 12 years) but the blood pressure, serum cholesterol concentration, and smoking history were not significantly different. The duration of exercise and haemodynamics were also similar in the two groups.

Usefulness of the non-invasive investigations

Table 6 gives the results of the non-invasive investigations for the 35 patients who had coronary arteriography and their sensitivity, specificity, positive predictive accuracy, negative predictive accuracy, and overall predictive accuracy.

Discussion

The similarity in the clinical course of patients with previous myocardial infarction and those with left ventricular hypertrophy and strain in the Framingham study has led to the suggestion that the electrocardiographic pattern typical of these conditions signified the onset of coronary artery disease.[4] As only half of the patients in our study who had coronary arteriography had coronary artery disease, however, this cannot be the only explanation for the electrocardiographic finding. The absence of obstruction to the epicardial coronary arteries does not of course exclude myocardial ischaemia. In patients with left ventricular hypertrophy and normal coronary arteries, typical angina[20-22] and objective signs of myocardial ischaemia[23-26] are well recognised. In the present study chest pain and non-invasive indicators of myocardial ischaemia

Table 6 Accuracy of the non-invasive investigations in predicting the presence of coronary artery disease (figures based on the 35 patients who had coronary arteriography)

	Sens (%)	Spec (%)	PPA (%)	NPA (%)	OPA (%)
Thallium scintigraphy:					
RPD	88·9	52·9	66·6	81·8	71·4
Exercise ECG:					
ST segment depression	50	70·6	64·3	57·1	60
Leads (No)	33·3	100	100	58·6	65·7
R wave	44·4	29·4	40·0	33·3	37·1
Two criteria	38·9	76·5	63·6	54·2	57·1
Three criteria	11·1	100	100	51·5	54·3
Ambulatory ECG:					
Channel I	33·3	64·7	50	47·8	48·6
Channel II	11·1	70·6	28·6	42·9	40
Both	5·6	76·5	20·0	43·3	40

Sens, sensitivity; Spec, specificity; PPA, positive predictive accuracy; NPA, negative predictive accuracy; OPA, overall predictive accuracy; RPD, reversible perfusion defect.

were present in five patients with left ventricular hypertrophy and normal coronary arteries. In total 43 patients had at least one episode of ambulatory ST segment depression consistent with myocardial ischaemia. As in a recent study of hypertensive patients with normal coronary arteries over 90% of these episodes were clinically silent.[26]

There are several factors that may be responsible for myocardial ischaemia in hypertensive left ventricular hypertrophy. There is a transmural gradient of blood flow in left ventricular hypertrophy with reduced flow in the subendocardial layers[27] that is accentuated by pacing[28] and exercise.[29] Although total myocardial blood flow is increased in left ventricular hypertrophy, the flow per 100 g is significantly reduced[30] because of decreased coronary vascular reserve[31] and perhaps disease of the small vessels.[22]

The ability of the coronary vasculature to maintain perfusion over a range of pressures may be altered by left ventricular hypertrophy.[32] Because oxygen extraction is almost maximal in the coronary circulation there is no mechanism, as there is in the cerebral circulation, whereby the effects of lower perfusion pressures can be compensated for by an increase in oxygen extraction.[33] This may be important during sleep when diastolic blood pressure often falls by up to 25%.[34] Certainly if the blood pressure is reduced by treatment to below the theoretical autoregulatory range, decreased coronary flow[35] and myocardial ischaemia[36] occur. Similar mechanisms have been proposed[37] as a possible explanation for the excess mortality found in some studies (but these are disputed by several workers) if treated diastolic blood pressure falls below 85–90 mm Hg—the so-called J shaped mortality curve.[38] The results of the present study are compatible with these theories and they emphasise the importance of myocardial ischaemia in patients with hypertensive left ventricular hypertrophy even in the absence of epicardial coronary artery disease.

Another important clinical question is how best to identify prognostically important coronary artery disease in hypertensive patients with left ventricular hypertrophy and strain. This is particularly relevant because most of the myocardial ischaemia in this study did not cause symptoms. Ambulatory monitoring of the ST segment has been shown to be useful in detecting symptomatic and silent myocardial ischaemia in patients with ischaemic heart disease.[16 39] It is a reproducible technique[40] and may provide prognostic information.[41] In patients with left ventricular hypertrophy and strain, however, investigations that rely on the electrocardiogram are difficult to interpret because of baseline electrocardiographic abnormalities. For example in this study nearly all the patients who had ambulatory electrocardiographic monitoring showed ST segment depression in channel I for most of the day. For this reason an arbitrary criterion of >0·2 mV additional ST segment depression over and above the baseline depression was required before interpretation as a positive result. Another potential problem with ambulatory ST monitoring is the frequency of ST segment shift in normal subjects.[42] It is likely that both these factors contributed to the low positive predictive accuracy (28·6–50%) of the ambulatory electrocardiography in the present study.

There were similar problems with the interpretation of the exercise electrocardiography. If conventional criteria[11] had been used virtually all patients would have had a positive test. The high rate of false positive results in patients with abnormal control electrocardiograms is well known[43] and we therefore decided to consider a change significant if there were changes additional to the resting ST segment depression, in order to improve the specificity of the test.[13] Analysis of the R wave amplitude with exercise may also improve the accuracy of exercise electrocardiography in patients with resting ST-T changes[12 14] and this was therefore incorporated into this study along with a comparison of the number of leads showing ST segment depression before and after exercise. The use of all these criteria combined resulted in 100% specificity but this was at the expense of sensitivity as only two patients with coronary artery disease had a test that was positive for all criteria (11·1% sensitivity). When sensitivity was improved by using only ST (50%) or R wave (44·4%) criteria the specificity was reduced (70·6% and 29·4% respectively).

In our group of patients, thallium scintigraphy was the most useful method for the identification of coronary artery disease. The sensitivity was 88·9%, which is comparable with reported series of patients with ischaemic heart disease in our hospital[17] and elsewhere.[44] The specificity of 52·9% was much less than for patients with ischaemic heart disease (89–97%).[44] The discrepancy is presumably due to the presence of myocardial ischaemia despite normal coronary arteries.

It is not possible from our results to determine whether the "false" positive non-invasive tests are such or are actually correctly identifying areas of ischaemia caused by left ventricular hypertrophy even in the absence of coronary artery disease. Two studies published recently, however, accord with our own results suggesting that the non-invasive findings are caused by myocardial ischaemia in these patients.[26 45] In terms of excluding epicardial coronary artery disease the negative predictive accuracy is perhaps the most useful criterion to assess the value of the test. Our results showing a negative predictive accuracy of 81·8% accord with those of Tubau *et al* who reported that over a 38 month period of follow up the negative predictive value of thallium scintigraphy for the subsequent development of angina symptoms was 94%.[46]

In summary, our results have shown that not all patients with left ventricular hypertrophy and strain have obstructive coronary artery disease. Non-invasive indicators of myocardial ischaemia are common in patients with left ventricular hypertrophy and strain even in those without symptoms or coronary artery disease. Symptoms of chest pain during exercise or during normal daily activities are poor indicators of the presence of myocardial ischaemia and much of this ischaemia is silent. Thallium perfusion scintigraphy is a useful investigation for the identification of coronary artery disease in these patients.

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1 Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: The Framingham Study. *Ann Intern Med* 1970;72:813–22.
2 Kannel WB. Prevalence and natural history of electrocardiographic left ventricular hypertrophy. *Am J Med* 1983;75 (suppl 3A):4–11.
3 Dunn FG, McLenachan J, Isles CG, *et al.* Left ventricular hypertrophy and mortality in hypertension: an analysis of data from the Glasgow Blood Pressure Clinic. *J Hypertens* 1990;8:775–82.
4 Kannel WB, Abbott RD. A prognostic comparison of left ventricular hypertrophy and unrecognised myocardial infarction: The Framingham Study. *Am Heart J* 1986; 111:391–7.
5 Macfarlane PW. British Regional Heart Study: the electrocardiogram and risk of myocardial infarction on follow-up. *J Electrocardiol* 1987;20 (suppl):53–6.
6 Pringle SD, Macfarlane PW, McKillop JH, Lorimer AR, Dunn FG. Pathophysiological assessment of left ventricular hypertrophy and strain in asymptomatic patients with essential hypertension. *J Am Coll Cardiol* 1989;13:1377–81.
7 Macfarlane PW, Watts MP, Podolski M, Shoat D, Lawrie TDV. The new Glasgow system. In: Willems JL, van Bemmel JH, Zyweitz C, eds. *Computer ECG analysis: towards standardisation*. Amsterdam: Elsevier, 1986:31–6.
8 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 1977;55:613–8.
9 Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 1960;49(suppl 169):45–60.
10 Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85: 546–62.
11 Martin CM, McConachy DR. Maximal treadmill exercise electrocardiography. Correlations with coronary arteriography and cardiac haemodynamics. *Circulation* 1972;46: 956–62.
12 Yiannikas J, Marcomichelakis J, Taggart P, Kelly BH, Emanuel R. Analysis of exercise-induced changes in R wave amplitude in asymptomatic men with electrocardiographic ST-T changes at rest. *Am J Cardiol* 1981; 47:238–43.
13 Kansal S, Roitman D, Sheffield LT. Stress testing with ST segment depression at rest. *Circulation* 1976;54:636–9.
14 Bonoris PE, Greenburg PS, Cristison GW, Castellanet MJ, Ellestad MH. Evaluation of R wave amplitude changes versus ST-segment depression in stress testing. *Circulation* 1978;57:904–10.
15 Macfarlane PW, McLung JM, Irving A, Watts MP, Taylor TP, Lawrie TDV. Computer assisted analysis of dynamic (24-hour) electrocardiograms. In: Macfarlane PW, ed. *Progress in electrocardiology*. London: Pitman, 1979: 123–6.
16 Mulcahy D, Keegan J, Cunningham D, *et al.* Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. *Lancet* 1988;ii:755–9.
17 Martin W, Tweddel AC, McGhie AI, Hutton I. Gated thallium scintigraphy in patients with coronary artery disease: an improved planar imaging technique. *Clin Phys Physiol Meas* 1987;8:343–54.
18 Swinscow TDV. *Statistics at square one*. 8th ed. Plymouth: Latimer and Trend, 1987.
19 Bradfield JWB, Beck G, Vecht RJ. Left ventricular apical thin point. *Br Heart J* 1977;39:806–9.
20 Baxter RH, Reid JM, McGuiness JB, Stevenson JG. Relation of angina to coronary artery disease in mitral and in aortic valve disease. *Br Heart J* 1978;40:918–22.
21 Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve. A mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *N Engl J Med* 1982;307:1362–7.
22 Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histological evidence for small vessel coronary artery disease in patients with angina and patent large coronary arteries. *Circulation* 1986;74:964–72.
23 Bailey IK, Come PC, Kelly DT, *et al.* Thallium-201 myocardial perfusion imaging in aortic valve stenosis. *Am J Cardiol* 1977;40:889–99.
24 McKillop JH, Murray RG, Turner JG. Thallium-201 imaging in aortic valve disease. *Nuklearmedizin* 1979; suppl 16:458–60.
25 Nagata S, Park Y, Minamikawa T, *et al.* Thallium perfusion and cardiac enzyme abnormalities in patients with familial hypertrophic cardiomyopathy. *Am Heart J* 1985;109: 1317–22.
26 Scheler S, Motz W, Vester J, Strauer BE. Transient myocardial ischaemia in hypertensive heart disease. *Am J Cardiol* 1990;65:51G–5G.
27 Rembert JC, Kleinman LH, Fedor JM, Wechsler AS, Greenfield Jr JC. Myocardial blood flow distribution in concentric left ventricular hypertrophy. *J Clin Invest* 1978;62:379–86.
28 Mueller TM, Marcus ML, Kreber RE, Young JA, Barnes RW, Abboud FM. Effects of renal hypertension and left ventricular hypertrophy on the coronary circulation in dogs. *Circ Res* 1978;4:543–9.
29 Murray PA, Vatner SF. Abnormal coronary vascular response to exercise in dogs with severe right ventricular hypertrophy. *J Clin Invest* 1981;67:1314–23.
30 Johnson LL, Sciacca RR, Ellis K, Weiss MB, Cannon PJ. Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. *Circulation* 1978;57:582–90.
31 Strauer B. Ventricular function and coronary hemodynamics in hypertensive heart disease. *Am J Cardiol* 1979; 44:999–1006.
32 Harrison DG, Florentine MS, Brooks LA, Cooper SM, Marcus ML. The effect of hypertension and left ventricular hypertrophy on the lower range of coronary autoregulation. *Circulation* 1988;77:1108–15.
33 Strangaard S, Haunso S. Why does antihypertensive treatment prevent stroke but not myocardial infarction? *Lancet* 1987;ii:658–61.
34 Miller-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. *Lancet* 1978;i:595–7.
35 Laskey WH, Zeevi GR, St John Sutton M, Martin JL, Hirshfeld JW, Reichek N. Effects of nitroglycerin in patients with angina, normal coronary arteries, and left ventricular hypertrophy. *Am Heart J* 1986;112:953–62.
36 Pepi M, Alimento M, Maltagliati A, Tosi E, Guazzi MD. Electrocardiographic alterations suggestive of myocardial injury elicited by rapid pressure lowering in hypertension. *Eur Heart J* 1988;9:889–905.
37 Floras JS. Antihypertensive treatment, myocardial infarction and nocturnal myocardial ischaemia. *Lancet* 1988;ii:994–6.
38 Cruickshank JM. Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *BMJ* 1988;297:1227–30.
39 Deanfield JE, Maseri A, Selwyn AP, *et al.* Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983;ii:753–8.
40 Khurmi NS, Raftery EB. Reproducibility and validity of ambulatory ST segment monitoring in patients with chronic stable angina pectoris. *Am Heart J* 1987;113: 1091–6.
41 Stern S, Tzivoni D. Early detection of silent ischaemic heart disease by 24-hour electrocardiographic monitoring of active subjects. *Br Heart J* 1974;36:481–6.
42 Kohli RS, Cashman PMM, Lahiri A, Raftery EB. The ST segment of the ambulatory electrocardiogram in a normal population. *Br Heart J* 1988;60:4–16.
43 Harris CN, Aronow WS, Parker DP, Kaplan MA. Treadmill stress test in left ventricular hypertrophy. *Chest* 1973; 63:353–7.
44 Stolzenberg J, London R. Stress thallium-201 scanning in coronary artery disease. *Med Clin North Am* 1980;64: 149–62.
45 Yurenev AP, de Quattro V, Devereux RB. Hypertensive heart disease: relationship of silent ischemia to coronary artery disease and left ventricular hypertrophy. *Am Heart J* 1990;120:928–33.
46 Tubau JF, Szlachcic J, Hollenberg M, Massie BM. Usefulness of Thallium-201 scintigraphy in predicting the development of angina pectoris in hypertensive patients with left ventricular hypertrophy. *Am J Cardiol* 1989; 64:45–9.

Br Heart J 1992;67:383–6

Circulating endothelin in acute ischaemic syndromes

Simon G Ray, John J McMurray, James J Morton, Henry J Dargie

Abstract

***Background*—Endothelin is an extremely potent vasoconstrictor that may have a role in the pathogenesis of acute myocardial ischaemia. Atrial natriuretic factor is an endogenous antagonist of endothelin. To find the pattern and possible importance of circulating endothelin in ischaemic heart disease, concentrations in normal controls and those in patients with stable and unstable angina, acute myocardial infarction, and chronic cardiac failure were compared. The relation between circulating concentrations of endothelin and atrial natriuretic factor in the aftermath of myocardial infarction was also examined.**

***Methods*—Eighteen patients with acute myocardial infarction, 10 with unstable angina, 10 with stable angina, 12 with chronic cardiac failure, and 10 normal controls were studied. Endothelin concentration was measured in venous plasma by radioimmunoassay. In patients with acute myocardial infarction simultaneous concentrations of endothelin and atrial natriuretic factor were measured on admission and at one, four, and 24 hours.**

***Results*—Mean concentrations (SEM) of endothelin were 5·72 (0·19) fmol/ml in controls, 6·56 (0·48) fmol/ml in stable angina, 6·41 (0·48) fmol/ml in unstable angina, and 13·83 (0·95) fmol/ml in chronic cardiac failure. In acute myocardial infarction concentrations were 8·81 (0·69) fmol/ml on admission, 11·85 (1·02) fmol/ml at one hour, 11·88 (1·10) fmol/ml at four hours, and 7·30 (0·49) fmol/ml at 24 hours. Concentrations of atrial natriuretic factor at the same times were 68·1 (13·1) pg/ml, 8·4 (1·5) pg/ml, 24·4 (4·1) pg/ml, and 42·0 (6·9) pg/ml.**

***Conclusions*—Plasma endothelin is raised in chronic heart failure and in the aftermath of acute myocardial infarction but not in stable or unstable angina. After myocardial infarction endothelin concentrations are raised whereas concentrations of atrial natriuretic factor are relatively low. The role of endothelin in the pathogenesis of acute myocardial infarction and its interactions with other humoral factors require further investigation.**

The endothelins are a family of three isopeptides that are extremely potent vasoconstrictors both in vivo and in vitro.[1 2] The development of sensitive assays has allowed the measurement of the low concentrations of endothelin circulating in plasma, and raised concentrations have been shown in a number of conditions including renal failure,[3] subarachnoid haemorrhage,[4] and after major surgery,[5] cardiogenic shock,[6] and acute myocardial infarction.[7–9] Little is known about the release of endothelin in ischaemic heart disease although left ventricular dysfunction, damage to the endothelium, and activation of coagulation and platelets have been suggested as possible stimuli.[7 9] Little is known, furthermore, of the relation between endothelin concentrations and those of other vasoactive hormones, particularly atrial natriuretic factor, which antagonises the vasoconstrictive effects of endothelin.[10]

To find the pattern and possible significance of circulating endothelin in ischaemic heart disease we compared concentrations in normal controls with those in patients with stable and unstable angina, acute myocardial infarction, and chronic cardiac failure. We also examined the relation between circulating concentrations of endothelin and atrial natriuretic factor in the aftermath of myocardial infarction.

Patients and methods

The study group consisted of 10 normal controls, 10 patients with unstable angina, 10 patients with stable angina, 12 patients with established cardiac failure, and 18 patients with acute myocardial infarction. All patients with stable angina had a history of at least three months of exercise induced chest pain, a positive Bruce protocol exercise test and >50% stenosis of at least one epicardial artery. Patients with unstable angina had pain at rest lasting for at least 10 minutes on two or more occasions accompanied by reversible electrocardiographic changes but no rise in cardiac enzymes. These patients were sampled within four hours of the last episode of pain. Patients with established cardiac failure were in New York Heart Association class (NYHAC) III or IV (six with ischaemic cardiomyopathy and six with valvar heart disease). All patients with acute myocardial infarction were admitted within six hours of chest pain with at least 2 mm ST segment elevation in two or more contiguous electrocardiographic leads. All received 1·5 MU of streptokinase intravenously over 45 minutes. None had had a previous myocardial infarction and all were in Killip class 1. All patients gave informed

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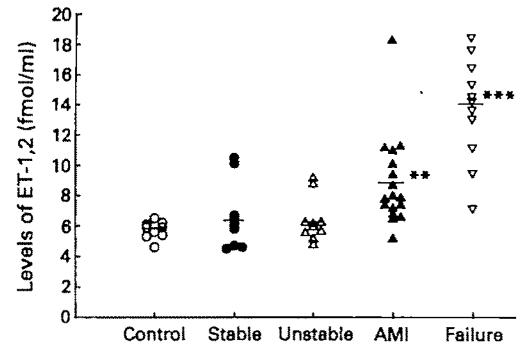

*Figure 1 Individual plasma concentrations of endothelin (ET-1,2) in controls and patients with stable and unstable angina, acute myocardial infarction (AMI), and established cardiac failure. Values for infarct patients are those taken on admission. **p < 0·01, ***p < 0·001 compared with controls.*

consent and the study was approved by the hospital ethics committee.

All blood samples were taken from an indwelling forearm venous canula after the patient had been resting in a semisupine position for at least 15 minutes. Blood was taken into chilled potassium EDTA tubes on ice and centrifuged at 3000 rpm for 10 minutes at 4°C within five minutes of venepuncture. Plasma was stored at −70°C until assay. In patients with myocardial infarction, serial samples were taken on admission, and at one, four, and 24 hours.

Endothelin was assayed using a radioimmunoassay system (Amersham International, Endothelin-1, 2(^{125}I) assay).[11] The antibody used has 100% cross reactivity with endothelin-1, 204% with endothelin-2, 0·024% with endothelin-3, and 38% with big endothelin-1. The lower limit of detection is 0·5 fmol/ml (1 fmol/ml = 2·5 pg/ml). Atrial natriuretic factor was assayed using a minor modification of the method of Richards *et al*, normal range 5–50 pg/ml (1 pg/ml = 0·32 pmol/l).[12]

Results are expressed as the mean (SE). Data were analysed by paired or unpaired Student's *t* tests with the Bonferroni correction for multiple comparisons as appropriate.[13]

Results

Figure 1 shows that mean concentrations of endothelin in patients with stable angina (6·56 (0·71) fmol/ml) and unstable angina (6·41 (0·48) fmol/ml) did not differ from normal (5·72 (0·19) fmol/ml). Mean concentration in patients with cardiac failure (13·83 (0·95) fmol/ml) was significantly higher than in the controls (p < 0·001). The table shows that for patients with acute myocardial infarction endothelin concentrations were highest at four hours and differed significantly from normal on admission (p < 0·01), at one hour (p < 0·01), and at four hours (p < 0·01). The peak concentration of endothelin did not correlate with maximal creatine kinase activity.

Table Individual plasma endothelin concentrations (fmol/ml) in patients with myocardial infarction

	On admission	*1 h*	*4 h*	*24 h*
	7·2	6·8	—	5·4
	7·4	9·0	8·8	6·0
	9·4	9·8	—	—
	5·2	9·1	7·2	7·0
	7·4	8·1	8·0	6·0
	6·8	8·0	9·7	9·2
	8·7	9·1	12·3	8·6
	7·9	7·1	10·7	6·6
	11·3	10·9	19·4	—
	10·1	12·7	10·7	—
	7·8	12·3	11·6	—
	6·6	14·1	9·6	6·5
	11·2	13·0	11·8	8·8
	7·8	—	14·8	6·8
	8·0	16·0	10·1	5·3
	6·5	14·7	7·0	6·0
	18·3	20·3	23·2	8·0
	11·0	20·4	15·2	12·0
Mean (SEM)	8·81 (0·69)	11·85 (1·02)	11·88 (1·10)	7·3 (0·49)

Concentrations of atrial natriuretic factor were raised on admission but declined abruptly at one hour, remaining below admission values at 24 hours. In 11 patients with acute myocardial infarction who had simultaneous measurements of both peptides, the fall in concentrations of atrial natriuretic factor coincided with the rise in endothelin (fig 2).

Discussion

This study shows that plasma endothelin concentrations are raised in the acute phase of myocardial infarction. Salminen *et al* found a similar pattern of endothelin concentrations in the immediate post infarction period with concentrations peaking at one to four hours and then declining.[9] Even at 72 hours, however, concentrations were above those in normal controls. Two other groups have described sustained rises in endothelin concentrations for at least three days after infarction though in both cases the highest concentrations were found on admission.[7 8] This prolonged increase may be accounted for by the inclusion of patients with more severe degrees of left ventricular failure than in the present study.

The exact role of endothelin in the pathogenesis of myocardial infarction remains undefined. It is undoubtedly an extremely potent vasoconstrictor of both coronary and systemic vessels. This effect could initiate or aggravate acute myocardial ischaemia. Whether circulating concentrations of endothelin in humans reach those sufficient to induce vasoconstriction is uncertain. Infusion of endothelin-1 in humans produces a significant rise in blood pressure at plasma concentrations seven times the preinfusion level[14] and concentrations of 3×10^{-10} mol/l to 3×10^{-9} mol/l contract human arteries in vitro.[15–17] Plasma endothelin concentrations in our infarction patients did not approach these values. This does not rule out a role for endothelin in the pathophysiology of infarction. The primary role of endothelin may be as an autacoid, acting

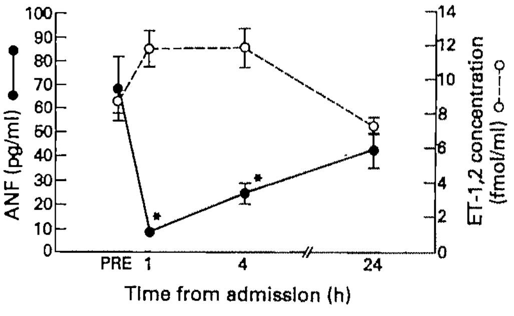

*Figure 2 Simultaneous mean (SEM) concentrations of atrial natriuretic factor (ANF), and endothelin (ET-1,2) from admission (n = 11). *p < 0·05 compared with admission. The error bars for ANF at one hour are within the filled circle.*

locally on vascular smooth muscle, with the circulating peptide resulting from spillover into the vascular lumen.[18 19] If so, then locally released endothelin may have a profound effect on vascular tone despite subthreshold concentrations in plasma. A role for endothelin in evolving myocardial infarction is strongly supported by studies of coronary ligation in the rat. In this model myocardial endothelin content increases after infarction and the extent of ventricular damage is reduced by the use of endothelin antibodies.[20]

Our finding of a negative correlation between concentrations of endothelin and atrial natriuretic factor deserves further comment. A number of authors including ourselves have previously described a fall in circulating atrial natriuretic factor in the immediate aftermath of myocardial infarction.[21–23] Superfusion of endothelin in atrial cell culture or infusion into intact animals leads to secretion of atrial natriuretic factor.[24 25] In turn atrial natriuretic factor both decreases the release of endothelin from cultured endothelial cells[26] and antagonises its vasoconstrictor effects,[10] thus closing a negative feedback loop and acting as a potential physiological antagonist. The effect of a small rise in circulating endothelin may be magnified by a simultaneous fall in atrial natriuretic factor. Endothelin also interacts synergistically to potentiate noradrenaline induced contractions of coronary arteries and adrenaline increases endothelin release from cultured porcine endothelial cells.[27 28] It is important that changes in endothelin concentrations are considered in the light of other changes in the hormonal milieu that may potentiate its effects.

Several factors may contribute to the increase of endothelin after acute myocardial infarction. Yasuda *et al* showed that concentrations of β thromboglobulin and thrombin-antithrombin III complex correlated with plasma endothelin concentration after infarction.[7] It is also known that thrombin increases endothelin production in cultured endothelial cells.[29] If activation of the clotting system were the primary cause of the rise in endothelin, higher concentrations would also have been expected in unstable angina, where platelets are activated and a thrombus forms within coronary arteries.[30 31] This was not the case in the present study, and Stewart *et al* have recently described normal concentrations of endothelin in coronary sinus plasma from patients with unstable angina.[32] Similarly myocardial ischaemia and disruption of the coronary endothelium due to plaque rupture are unlikely to be principal causes as they too are common to both unstable angina and myocardial infarction.[31 33] Endothelin concentrations are raised in other situations of acute stress, such as major surgery, and may reflect a non-specific response.[5] In keeping with this hypothesis Miyauchi *et al* have shown that the human pre-proendothelin-1 gene contains sequences related to the acute phase reactant response.[8]

Endothelin concentrations are known to rise on standing, presumably as a response to hypotension.[34] Streptokinase induces hypotension in a proportion of patients but this is usually transient and whereas it is possible that it may have influenced endothelin levels at one hour it is unlikely to have a sustained effect.[35] To ensure a homogenous population of patients with acute myocardial infarction only streptokinase treated patients were included in this study. We are therefore unable to comment on the influence of thrombolysis itself on concentrations of endothelin or atrial natriuretic factor. Reduced renal clearance of endothelin probably accounted at least in part for the high values in the patients with established cardiac failure, though other factors such as widespread endothelial dysfunction of the peripheral circulation cannot be ruled out.[36] These mechanisms are unlikely to have been operative in our patients with myocardial infarction, none of whom had clinically evident cardiac failure.

The concentrations of plasma endothelin in our control group were similar to those reported by Davenport *et al* using the same assay.[11] They are, however, considerably higher than those obtained by other assays,[6–8] presumably as a result of differing cross reactivities of the antibodies used against the endothelin isopeptides and to big endothelin. These differences must be borne in mind when comparing our results with those of other workers.

We conclude that plasma concentrations of endothelin are raised within six hours of uncomplicated myocardial infarction. These values are probably not high enough to induce vasoconstriction alone but may do so in combination with other humoral factors. A number of mechanisms could contribute to this rise in endothelin but the exact cause remains uncertain.

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1 Yanagisawa M, Kurihara H, Kimura S, *et al*. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;332:411–5.

2 Inoue A, Yanagisawa M, Kimura S, *et al*. The human endothelin family: Three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc Natl Acad Sci USA* 1989;86:2863–7.

3 Schichiri M, Hirata Y, Ando K, *et al*. Plasma endothelin levels in hypertension and chronic renal failure. *Hypertension* 1990;15:493–6.

4 Masaoka H, Suzuki R, Hirata Y, Emori T, Marumo F, Hirakawa K. Raised plasma endothelin in aneurysmal subarachnoid haemorrhage. *Lancet* 1989;ii:1402(letter).

5 Saito T, Yaganisawa M, Miyauchi T, *et al*. Endothelin in human circulating blood: Effects of major surgical stress [abstract]. *Jpn J Pharmacol* 1989;49:215.

6 Cernacek P, Stewart DJ. Immunoreactive endothelin in human plasma: Marked alterations in cardiogenic shock. *Biochem Biophys Res Commun* 1989;161:562–7.

7 Yasuda M, Kuhno M, Tahara A. Circulating immunoreactive endothelin in ischaemic heart disease. *Am Heart J* 1990;119:801–6.

8 Miyauchi T, Yanagisawa M, Tomizawa T. Increased plasma concentrations of endothelin-1 and big endothelin -1 in acute myocardial infarction. *Lancet* 1989;ii:53–4.

9 Salminen K, Takkanen I, Saijonmaa O, Nieminen M, Fyhrquist F, Frick MH. Modulation of coronary tone in acute myocardial infarction by endothelin. *Lancet* 1989;ii:747.

10 Bonhomme M-C, Cantin M, Garcia R. Relaxing effect of atrial natriuretic factor on endothelin precontracted vascular strips. *Proc Soc Exp Biol Med* 1989;191:305–15.

11 Davenport AP, Ashby MJ, Easton P, *et al*. A sensitive radioimmunoassay measuring endothelin like immunoreactivity in human plasma: comparison of levels in patients with essential hypertension and normotensive control subjects. *Clin Sci* 1990;78:261–4.

12 Richards AM, Tonolo G, McIntyre GD, Leckie BJ, Robertson JIS. Radioimmunoassay for plasma alpha human atrial natriuretic peptide: A comparison of direct and pre-extracted methods. *J Hyperten* 1987;5:227–36.

13 O'Brien PC, Shampo MA. Statistical considerations for performing multiple tests in a single experiment. 5.

Comparing two therapies with respect to several endpoints. *Mayo Clin Proc* 1988;63:1140–3.

14 Vierhapper H, Wagner O, Nowotny P, Waldhausl W. Effect of endothelin-1 in man. *Circulation* 1990;81:1415–8.

15 Chester AH, Dashwood MR, Clarke JG. Influence of endothelin on human coronary arteries and localisation of its binding sites. *Am J Cardiol* 1989;63:1395–8.

16 Miyauchi T, Tomobe Y, Shiba R, *et al.* Involvement of endothelin in the regulation of human vascular tonus. *Circulation* 1990;81:1874–80.

17 Hughes AD, Thom A McG, Woodall N, *et al.* Human vascular responses to endothelin-1: observations in vivo and in vitro. *J Cardiovasc Pharmacol* 1989;13 (suppl 5):225–8.

18 Whittle BJR, Moncada S. The endothelin explosion. A pathophysiological reality or a biological curiosity. *Circulation* 1990;81:2022–5.

19 Yaganisawa M, Masaki T. Endothelin, a novel endothelium derived peptide. *Biochemical Pharmacology* 1989;38: 1877–83.

20 Wanatabe T, Suzuki N, Shimamato N, Fujino M, Imada A. Endothelin in myocardial infarction. *Nature* 1990; 344:144.

21 Ray SG, Leckie B, Findlay I, Raeside D, Northridge D, Dargie HJ. Changes in renin and atrial natriuretic during thrombolysis with streptokinase [abstract]. *Eur Heart J* 1989;10:277.

22 Tan ACITL, Van Loenhout TT, Lamfers EJP, *et al.* Atrial natriuretic peptide after myocardial infarction. *Am Heart J* 1989;118:490–4.

23 Svanegaard J, Angelo-Nielsen K, Pindborg T. Atrial natriuretic peptide and acute myocardial infarction. *Am Heart J* 1989;117:194–5.

24 Fukuda Y, Hirata Y, Yoshimi H, *et al.* Endothelin is a potent secretagogue for atrial natriuretic peptide in cultured myocytes. *Biochem Biophys Res Commun* 1988;155: 167–72.

25 Stasch JP, Hirth-Dietrich C, Kazda S, Neuser D. Endothelin stimulates release of atrial natriuretic peptide in vitro and in vivo. *Life Sci* 1989;45:869–75.

26 Fyhrquist F, Saijonmaa O, Metsarinne K, Sirvio ML. Atrial natriuretic peptide and nitroglycerine reduce endothelin secretion from cultured endothelial cells [abstract]. *Am J Hypertens* 1990;3:90.

27 Kohno M, Murakawa K, Yokokawa K, *et al.* Production of endothelin by cultured porcine endothelial cells: modulation by adrenaline. *J Hypertens* 1989;7 (suppl 6):130–1.

28 Yang Z, Richard V, von Segener L. Endothelin-1 potentiates contractions to nor-epinephrine and serotonin in human mammary and coronary arteries [abstract]. *J Am Coll Cardiol* 1990;15:12.

29 Emori T, Hirata Y, Ohta K, Schichiri M, Marumo F. Secretory mechanism of immunoreactive endothelin in cultured bovine endothelial cells. *Biochem Biophys Res Commun* 1989;160:93–100.

30 Fitzgerald DJ, Roy L, Catella F, Fitzgerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986;315:983.

31 Sherman CT, Litvack F, Grundfest W, *et al.* Coronary angioscopy in patients with unstable angina. *N Eng J Med* 1986;315:913–9.

32 Stewart JT, Nisbet JA, Davies MJ. Plasma endothelin in coronary venous blood from patients with either stable or unstable angina. *Br Heart J* 1991;66:7–9.

33 Davies MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischaemic death. *N Eng J Med* 1984;310:1137–40.

34 Schichiri M, Hirata Y, Ando K. Postural change and volume expansion affect plasma endothelin levels. *JAMA* 1990;263:661.

35 Lew AS, Laramee P, Cercek B, Shah P, Ganz W. The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction. *Circulation* 1985; 72:1321–6.

36 Kohno M, Murukawa K, Yasunari K, *et al.* Prolonged blood pressure elevation after endothelin administration in bilaterally nephrectomised rats. *Metabolism* 1989;38: 712–3.

Br Heart J 1992;67:387–91

Influence of age on the relation between heart rate variability, left ventricular ejection fraction, frequency of ventricular extrasystoles, and sudden death after myocardial infarction

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Abstract

***Aims*—To examine the influence of age on the prediction of sudden death after acute myocardial infarction based on heart rate variability (HRv), left ventricular ejection fraction (LVEF), and the frequency of ventricular extrasystoles.**

***Background*—Autonomic and left ventricular function and the frequency of ventricular extrasystoles change with age but the influence of age on the prediction of sudden death from these variables has not been examined.**

***Methods*—The 477 patients who had been through an early postinfarction risk stratification protocol and followed up for a mean of 790 days were dichotomised at 60 years of age.**

***Results*—Sudden deaths occurred with similar frequency in both age groups (12 (4·7%) of the 256 patients aged <60 years and seven (3·2%) of the 221 older patients). Sudden death, however, accounted for 52% of all deaths in the young group but only 18·4% of all deaths in the older group ($p < 0·01$). An HRv index of <20 units combined with an average of more than 10 ventricular extrasystoles an hour on Holter monitoring (VE10) had a sensitivity of 50%, a positive predictive accuracy of 33%, and a risk ratio of 18 in the young group ($p < 0·001$) but was not significantly predictive in older patients. The situation was similar when the combination of an LVEF <40% with VE10 was considered. This combination had a sensitivity of 44%, positive predictive accuracy of 36·4%, and a risk ratio of 16·1 in young patients ($p < 0·001$), but was not significantly predictive in older patients. The combination of VE10 with either LVEF <40% or HRv <20 units gave a sensitivity of 75%, positive predictive accuracy of 30%, and a risk ratio of 30 in young patients ($p < 0·001$), but the relation between this combination and sudden death in older patients was not statistically significant.**

***Conclusion*—In postinfarction patients aged <60 sudden death was a more predominant mode of death and was more reliably predicted from a depressed HRv index, an LVEF <40%, and VE10 than in older postinfarction patients. These findings may have important implications for post-infarction risk stratification and management.**

Left ventricular dysfunction and frequent ventricular extrasystoles are associated with an increased risk of sudden death after myocardial infarction.[12] The clinical value of this relation, however, is still questioned partly because it is unclear how these variables cause sudden death. The association between autonomic dysfunction and ventricular fibrillation in animals[3] has recently generated interest in the potential of autonomic function tests to predict and explain sudden death in postinfarction patients. Firstly, Kleiger *et al*[4] showed that depressed heart rate variability was associated with increased all cause mortality after myocardial infarction and La Rovere *et al*[5] and Farrell *et al*[6] subsequently showed a correlation between reduced baroreceptor sensitivity and an increased risk of sudden death and ventricular arrhythmias in postinfarction patients.

There is a decline in autonomic function with age in both postinfarction patients and in healthy controls.[7–9] Age is also a well recognised determinant of all cause mortality after myocardial infarction.[10–12] But as autonomic function,[7–9] ventricular systolic,[13] and diastolic function,[14–16] and the prevalence of frequent ventricular extrasystoles[17] all change with age, their value as predictors of sudden death may well change with age. We examined the practical implications of this hypothesis by dichotomising 477 serial postinfarction patients at 60 years of age.

Patients and methods

PATIENTS

The study population consisted of 477 patients under the age of 75 years admitted to our institution with acute myocardial infarction. Acute myocardial infarction was diagnosed if two of three criteria were met:

(*a*) Characteristic chest pain lasting 30 minutes.
(*b*) A sequential rise and fall in plasma concentrations of aspartate transaminase, β hydroxy-

butyric dehydrogenase, or creatine kinase with a peak concentration at least twice the upper limit of the reference range of our laboratory.
(*c*) Development of new pathological Q waves or persistent ST-T changes suggestive of non-Q wave infarction.

Only patients admitted straight from home and who survived the acute phase of myocardial infarction were enrolled in the study and studied prospectively.

EVALUATION

As part of the risk stratification protocol, the patients' historical and clinical data on admission were recorded and following tests were performed between five and 11 days after infarction:
(*a*) Ambulatory 24 hour electrocardiographic recordings with a Reynolds Tracker two channel recorder (leads II and CM5). We used the Pathfinder 3 system, an operator-computer interactive device, for arrhythmia recognition and grading ventricular frequency.
(*b*) Patients performed a symptom limited treadmill exercise test with the Bruce protocol just before discharge from hospital. Exercise-induced ST segment depression, angina, or ventricular tachycardia; a rise in systolic blood pressure of less than 30 mm Hg; or an inability to complete the first stage of the protocol were indications for predischarge left ventriculography and selective coronary angiography. Left ventricular ejection fraction (LVEF) was calculated from the ventricular silhouettes at end systole and end diastole in the right anterior oblique view by a digitising personal computer program (MAC angio computer package) based on the formula of Sandler and Dodge.[18] In those patients who did not undergo coronary angiography, radionuclide angiograms were performed in the supine position and the LVEFs were calculated by the multiple gated method performed in the 45° left anterior oblique projection.[19]

FOLLOW UP

All patients were followed up in a special infarct clinic. Follow up visits were made three to four weeks after discharge from hospital, then at three months, and subsequently every year or more frequently when clinically indicated. Treatment was at the discretion of the patient's physician. β Blockers and antiarrhythmic therapy were not routinely prescribed. The main endpoint was sudden death, which was classified by OO and TF without knowledge of the risk stratification results. Sudden death was defined as death within an hour of the onset of new symptoms: it included instantaneous deaths, deaths during sleep, and unwitnessed death, provided these occurred within an hour of the patient last being seen.[20] It was confirmed by examination of the case records, by the results of necropsy when available, and by interviewing the relatives or the general practitioner.

Table 1 Clinical and historical characteristics and distribution of prognostic variables

	Age < 60 (n = 256)	*Age ≥60 (n = 221)*	*p Value*
	Clinical and historical characteristics (n (%)		
Past MI	21 (8·2)	45 (20·4)	$p < 0\cdot001$
Anterior MI	120 (46·9)	98 (44·3)	
Non-Q wave MI	103 (40·2)	75 (34·0)	
Streptokinase	112 (43·8)	94 (42·5)	
Aspirin	119 (46·5)	109 (49·3)	
β blockers on discharge	110 (43·0)	58 (26·2)	$p < 0\cdot001$
Revascularisation	66 (25·8)	39 (17·7)	$p < 0\cdot05$
	Distribution of prognostic variables		
Age (y (SEM))	51·1 (0·43)	66 (0·25)	
HRv <20 (no (%))	40 (17·9)	63 (32·3)	$p < 0\cdot001$
HRv (mean (SEM))	28·8 (0·71)	24·8 (0·8)	$p < 0\cdot0001$
LVEF < 40% (n(%))	51 (21·9)	62 (30·5)	$p < 0\cdot05$
LVEF (mean (SEM)	51·8 (0·9)	47·5 (1·1)	$p < 0\cdot004$
VE10 (n(%))	38 (17·0)	55 (28·2)	$p < 0\cdot01$

MI, myocardial infarction; HRV < 20, heart rate variability under <20 units; LVEF, left ventricular ejection fraction; VE10, ventricular extrasystoles of 10 or more per hour.

ANALYSIS

A heart rate variability index (HRv) was calculated by digitising the 24 hour electrocardiographic recording off line and transferring it to a personal computer (IBM PC-AT). Each beat was then classed as normal or aberrant based on the matching pairs principle. An HRv was calculated for each patient.[21 22] The frequency distribution of durations of normal to normal RR intervals was constructed. Measured values of HRv were then obtained in technical units by measuring the baseline width of the distribution curve. This method of triangular interpolation of the frequency distribution of the normal to normal interval duration, which has been explained in more detail elsewhere,[23 24] is not affected by low levels of noise and artefact, whereas the widely used methods based on the standard deviation of normal to normal interval durations require the long term electrocardiogram to be clear of artefacts.[21]

To show the strength of associations we selected a LVEF cut off of 40%. Previous studies have shown a close association between a frequency of ventricular extrasystoles of ≥ 10 per hour (VE10) and sudden death.[1 2] A cut off point of 20 baseline width units was selected for the HRv because our previous study had shown that this value best distinguished patients with arrhythmic events from those without.[24] The population was divided at the age of 60 because this gave nearly the same number of patients and the same rates of sudden death in each group.

The HRv was calculated in 418 patients; left ventricular angiography carried out in 436 patients; and 409 patients had data for both. Predictive characteristics were calculated for the appropriate subtotals.

The χ^2 test with Yates' correction and *t* tests was used to determine the significance of the differences between proportions and means respectively. A value of $p < 0\cdot05$ was considered to be significant.

Results

There were 343 (71·9%) men and 134 (28·1%) women aged between 26 and 75 (mean (SD), 57·6 (9·4) years. Of the 477 patients, 221 were 60 or older and 256 were younger than 60. A higher proportion of older patients (20·4%) than younger patients (8·2%) had a history of previous infarction ($p < 0\cdot001$) but more

Table 2 Relation between clinical variables and sudden death (n (sudden deaths))

	Age <60	*Age ≥60*
Past MI	21 (3)	45 (1)
Anterior MI	120 (4)	98 (5)
Non-Q-wave MI	103 (6)	75 (2)
Streptokinase	112 (2)	94 (2)
Killip >2	10 (0)	32 (4)
Congestive failure	12 (1)	33 (2)
β blockers on discharge	110 (1)	58 (1)
HRv < 20 units	40 (6)	63 (5)
LVEF < 40%	51 (5)	62 (2)
VE10	38 (6)	55 (2)
HR > 80/min	202 (7)	168 (5)

See footnote to table 1 for abbreviations.

younger (43%), than older patients (26·2%) were discharged on β blockers (p < 0·01). Tables 1 and 2 show the other major historical and clinical characteristics.

ALL CAUSE MORTALITY AND SUDDEN DEATH RATES

The mean follow up period was 790 (range 490–1412) days during which there were 61 (12·8%) deaths, made up of 23 (9%) of the 256 younger patients and 38 (17·2%) of the 221 older patients (p < 0·02). There were 19 (4%) sudden deaths, made up of 12 (4·7%) of 256 in the young group, and seven (3·2%) of the 221 older patients (NS). Therefore, 12 (52%) of the 23 deaths in the young group and seven (18·4%) of the 38 deaths in the older group were sudden (p < 0·01).

TIMING OF SUDDEN DEATHS

Sudden deaths in younger patients occurred between seven and 373 days after infarction; seven (58·3%) occurred within 30 days of infarction. The sudden deaths in older patients occurred between 18 and 439 days of infarction with three (42%) occurring within 30 days of infarction.

Table 3 Relation of HRv and VE10 to sudden death

	n	*Sd*	*sens*	*ppa*	*rr*	*(95% CI)*	*p Value*
All patients (n = 418), sudden deaths = 14 (3·3%)							
HRv < 20	103	11	78·6	10·7	11·0	(3·2 to 39·3)	<0·001
VE10	93	8	57·0	8·6	4·7	(3·1 to 24·1)	<0·01
HRv < 20 + VE10	35	5	36·0	14·3	6·1	(2·2 to 17·3)	<0·01
Patients aged <60 (n = 223), sudden deaths = 8 (3·6%)							
HRv < 20	40	6	75·0	15·0	13·7	(2·9 to 65·4)	<0·001
VE10	38	6	75·0	15·8	15·4	(3·2 to 73·0)	<0·001
HRv < 20 + VE10	12	4	50·0	33·0	17·6	(5·0 to 62·2)	<0·001
Patients aged ≥60 (n = 195), sudden deaths = 6 (3·1%)							
HRv < 20	63	5	83·3	7·9	10·5	(1·3 to 88·2)	<0·05
VE10	55	2	33·0	3·6	2·6	(0·5 to 13·9)	NS
HRv < 20 + VE10	23	1	16·7	4·3	1·4	(0·2 to 11·5)	NS

Sd, sudden deaths; ppa, positive predictive accuracy; rr, risk ratio; sens, sensitivity.

Table 4 Relation of EF < 40 and VE10 to sudden death

	n	*Sd*	*Sens*	*ppa*	*rr*	*(95% CI)*	*p Value*
All patients (n = 436), sudden deaths = 15 (3·4%)							
LVEF < 40	113	7	46·7	6·2	2·5	(1·0–6·8)	NS
LVEF < 40 + VE10	37	5	33·0	13·5	5·4	(2·0–14·3)	<0·01
Patients aged <60 (n = 233), sudden deaths = 9 (3·9%)							
LVEF < 40	51	5	55·6	9·8	4·5	(1·3–16·0)	<0·05
LVEF < 40 + VE10	11	4	44·4	36·4	16·1	(3·9–69·4)	<0·001
Patients aged ≥60 (n = 203), sudden deaths = 6 (2·9%)							
LVEF < 40	62	2	33·3	3·2	1·1	(0·2–6 0)	NS
LVEF < 40 + VE10	26	1	16·7	3·8	1·4	(0·2–11·2)	NS

For abbreviations see footnotes to tables 1 and 3.

RELATION BETWEEN AN HRV INDEX < 20 UNITS AND SUDDEN DEATH

An HRv index <20 units was found in 40 (17·9%) of the young patients: six (15%) of these 40 compared with two (1%) of the 183 patients with HRv >20 units died suddenly (p < 0·001). An HRv <20 units was found in 63 (32·3%) of the older patients: five (7·9%) of these 63 compared with one (1%) of the 132 older patients with HRv >20 units died suddenly (p < 0·05) (table 3).

RELATION BETWEEN A LOW LVEF AND SUDDEN DEATH

An LVEF <40% was found in 51 (21·9%) of the 233 younger patients: five (10%) of these 51 compared with four (2%) of the 182 patients with EF ≥40% died suddenly (p < 0·05). An EF <40% was found in 62 (30·5%) of the 203 older patients: two (3·2%) of these 62 compared with four (2·8%) of the 141 patients with EF ≥40% died suddenly (NS) (table 4).

RELATION BETWEEN VE10 AND SUDDEN DEATH

Thirty eight (17%) of 223 young patients had VE 10: six (15·8%) of these 38 died suddenly compared with two (1%) of the remaining 185 patients (p < 0·001). VE10 was found in 55 (28·2%) of the older patients: two (3·6%) of these 55 patients and four (2·9%) of the remaining patients died suddenly (NS) (table 3).

RELATION BETWEEN THE COMBINATION OF VE10 AND HRV AND SUDDEN DEATH

A low HRv and VE10 were combined in 12 (5·4%) of the young patients: four (33%) of these 12 patients died suddenly compared with four (1·6%) of the remaining patients (p < 0·001). The relation between these variables and sudden death in older patients was not statistically significant (table 3).

RELATION BETWEEN SUDDEN DEATH AND THE COMBINATION OF A LOW LVEF AND VE10

An LVEF <40% was combined with VE10 in 11 (4·7%) of the young patients: four (36·4%) of these died suddenly compared with five (2·3%) of the remaining patients (p < 0·001). The relation between this combination of variables and sudden death in the older group did not reach statistical significance (table 4).

RELATION BETWEEN SUDDEN DEATH AND THE COMBINATION OF VE10 WITH LOW HRV OR LOW LVEF

A combination of VE10 with either a low HRv or an LVEF < 40% was found in 20 (9·1%) of the 236 young patients: six (30%) of these 20 died suddenly compared with two (1%) of the remaining patients (p < 0·001) (table 5). The relation between this combination of variables and sudden death did not reach statistical significance in the older group.

Discussion

We have shown that sudden death is a commoner mode of death and is more reliably

Table 5 Relation of LVEF and HRv to sudden death (Sd)

	n	*Sd*	*Sens*	*ppa*	*rr*	*(95% CI)*	*p Value*
All patients (n = 409), sudden deaths = 14 (3·4%)							
HRv + EF	42	5	35·7	11·9	4·9	(1·8–14·0)	<0·01
HRv/EF	174	13	92·8	7·5	17·6	(2·3–131·6)	<0·001
HRv/EF + VE10	52	7	50·0	13·5	6·9	(5·0–36·6)	<0·001
Patients aged <60 (n = 219), sudden deaths = 8 (3·7%)							
HRv + EF	12	3	37·5	25·0	10·4	(2·6–41·3)	<0·01
HRv/EF	79	8	100·0	10·0	—		<0·001
HRv/EF + VE10	20	6	75·0	30·0	30·0	(16·5–138·4)	<0·001
Patients aged >60 (n = 190), sudden deaths = 6 (3·2%)							
HRv + EF	30	2	33·0	6·7	2·7	(0·5–14·2)	NS
HRv/EF	95	5	83·3	5·3	5·0	(2·0–49·4)	NS
HRv/EF + VE10	32	1	16·7	3·1	1·0	(0·1–8·2)	NS

See footnotes to tables 1 and 3 for abbreviations.

predicted in younger than in older postinfarction patients by heart rate variability, frequency of ventricular extrasystoles, and to a lesser extent the left ventricular ejection fraction. Our first finding is consistent with previous reports. Vismara *et al*[25] who found that 36% of the deaths in postinfarction patients aged under 50 years but only 16% of the deaths in older patients were sudden. According to Daly *et al* 46% of deaths in 551 young men who survived unstable angina or acute myocardial infarction were sudden and the proportion of sudden deaths was inversely related to age at initial attack.[26]

The rates of sudden death (4%, 5·4%, and 4·5%) in our study and in the MILIS and BHAT studies are similar.[1,2] The higher proportion of patients with VE10 in our study (22%), however, compared with 15% and 13% reported by the MILIS and BHAT studies may be due to differences between the studies in criteria for patient recruitment, in the timing of Holter monitoring, and in the proportion of older patients.[1,2] The positive predictive accuracy of VE10 for sudden death in the present study of 8·6% was, nevertheless, close to the 10% and 9% reported by the MILIS and BHAT studies.[1,2]

The BHAT study found a direct relation between the frequency of ventricular extrasystoles and age; but the implications of this finding for risk stratification were not considered.[3] We found VE10 to be a more reliable predictor of sudden death in the younger patients (table 3). The combination of low HRv with VE10 was present in 8·5% of our patients and was also a much better predictor in the younger group (table 3).

An LVEF <40% had a positive predictive accuracy for sudden death of 6·2% in our study and of 10% in the MILIS study.[1] In a report in 1977 by Schulze *et al*,[27] 55% of the patients (compared with 26% in our study) had an LVEF <40%, a finding that had a positive predictive accuracy of 18%. In the study by Schulze *et al* all the sudden deaths occurred in patients with an LVEF <40%. But a rate of 14·7% for sudden deaths in patients taking quinidine or procainamide, compared with 6·4% in those not taking antiarrhythmic drugs, indicates that the relation between LVEF <40% and sudden death may have been reinforced by the concomitant arrhythmogenic effect of antiarrhythmic therapy in patients with low ejection fractions.

In the MILIS study 40 (7·5%) patients had both VE10 and a low LVEF.[1] This subgroup was older than the other subgroups of patients and contained 24% of all the sudden deaths. If, however, older patients are more likely than younger patients to have frequent ventricular extrasystoles and to have had a previous infarction (and thus low LVEFs) the predictive characteristics of these variables may have been different in the younger members of this high risk subgroup. In our study about 5% of young patients had a low LVEF and VE10 and this combination had a sensitivity of 44% and a positive predictive accuracy of 36%. We also found that the combination of VE10 and a depressed HRv and the combination of VE10 with an LVEF <40%, though they had similar predictive characteristics, identified different patients at high risk of sudden death (tables 3 and 4). Even more striking was that the combination of VE10 with either low HRv or an LVEF <40% had a sensitivity of 75% and a positive predictive accuracy of 30% in young patients, and values of only 17% and 3% in the older group (table 5).

Our results may reflect the inadequacies of present techniques. Thus even if all the sudden deaths were due to autonomic dysfunction, the degree to which depressed heart rate variability accurately reflects this dysfunction seems to decline with age. This may be due to a considerable age related divergence between the effects of autonomic dysfunction on the sinus node and on the electrophysiology of the myocardium.

Our findings may also be the result of a decline with age in the proportion of sudden deaths caused by autonomic dysfunction. There are several possible mechanisms for this proposition:

(*a*) If the predisposition to ventricular fibrillation is brought about by the change in autonomic tone, rather than absolute autonomic level, older patients may experience less severe changes in sympathovagal balance after myocardial infarction than younger patients.

(*b*) Sympathetic denervation is associated with adrenergic hypersensitivity and an increased predisposition to ventricular fibrillation in dogs.[28] Preconditioning ischaemia prevents this sympathetic denervation. Subclinical ischaemia caused by more severe coronary disease and to decreased myocardial compliance[28] may have a similar protective effect in older patients. Also young patients have higher β receptor density and activity and less myocardial fibrosis than older patients[29,30] and may therefore be either more likely, for the same degree of sympathovagal imbalance, to reach the rapid rates at which ventricular tachycardia deteriorates into ventricular fibrillation or to reach such rates more quickly.[31]

(*c*) The relative importance of thromboembolic, rheological, ischaemic, and haemodynamic causes of sudden death increases with age.[32]

CLINICAL IMPLICATIONS

Whatever their explanation, our results indicate that it is not correct to assume physiological homogeneity in a postinfarction population. Such an approach will lead to young patients at higher risk of sudden death being overlooked and many older patients receiving inappropriate treatment.

LIMITATIONS OF THE STUDY

The dichotomy point of 60 years seems arbitrary and its physiological significance is unclear. It was chosen, however, because it provided nearly the same proportion of patients and the same rates of sudden death in each group. The relations between heart rate variability, frequency of ventricular extrasystoles, and sudden death remained significant even in patients younger than 55, among whom there was a sudden death rate of only 2·4%. Our use of VE10 as a prognostic variable was based on the results of previous studies,[1 2] but this variable may need to be refined: ventricular extrasystoles caused by increased sympathetic activity may have different prognostic implications from those triggered by increased wall stress. The LVEF may be refined by considering diastolic function and abnormalities of wall motion.

Only two of the 12 young and one of the seven older patients who died suddenly were taking β blockers but because β blocker therapy was uncontrolled its effect on our results is difficult to determine. The rates of sudden death may have been lower had more patients $\geqslant 60$ received β blockers.[33] The effect of thrombolytic therapy on our results and the effect of the difference in the proportion of young and old patients who had surgery or angioplasty is also unknown.

Nevertheless, we have shown that age influenced the prediction of sudden death after myocardial infarction based on autonomic function tests, left ventricular ejection fraction, and the frequency of ventricular extrasystoles. If confirmed, our findings could have significant implications for postinfarction risk stratification and management.

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1 Mukharji J, Rude R, Poole W, and the Milis Study Group. Risk factors for sudden death after acute myocardial infarction. Two-year follow-up. *Am J Cardiol* 1984;54:31–6.
2 Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C, for the BHAT Study Group. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *J Am Coll Cardiol* 1987;10:231–42.
3 Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari G, Billman G, Foreman DR. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988;78:969–79.
4 Kleiger RE, Miller PJ, Bigger JT, Moss A, and the Multicentre Postinfarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–62.
5 La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity. Clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 1988;78:816–24.
6 Farrell TG, Paul V, Cripps TR, Bennett ED, Ward D, Camm AJ. Baroreflex sensitivity and electrophysiological correlates in postinfarction patients. *Circulation* 1991;83:945–52.
7 Gribbin B, Pickering T, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in Man. *Circ Res* 1971;29:424–31.
8 Collins K, Exton-Smith A, James M, Oliver D. Functional changes in autonomic nervous responses with ageing. *Age Ageing* 1980;9:17–24.
9 Ingall TJ, McLeod J, O'Brien PC. The effect of ageing on autonomic nervous system function. *Aust NZ J Med* 1990;20:570–7.
10 Martin C, Thompson P, Armstrong B, Hobbs M, DeKlerk N. Long-term prognosis after recovery from myocardial infarction: a nine year follow up of the Perth Coronary Register. *Circulation* 1983;68:961–9.
11 Tofler G, Muller J, Stone P, Willich S, Davis V, Poole K, *et al* and the MILIS study group. Factors leading to shorter survival after acute myocardial infarction in patients aged 65 to 75 years compared with younger patients. *Am J Cardiol* 1988;62:860–7.
12 Peart I, Odemuyiwa O, Albers C, Hall A, Kelly C, Hall RJC. Exercise testing soon after myocardial infarction; its relation to course and outcome at one year in patients aged less than 55 years. *Br Heart J* 1989;61:231–7.
13 Port S, Cobb FR, Coteman FB, Jones RH. Effect of age on the response of the left ventricular ejection fraction to exercise. *N Engl J Med* 1980;303:1133–7.
14 Iskrandian AS, Hakki A. Age-related changes in left ventricular diastolic performance. *Am Heart J* 1986;112:75–8.
15 Hodkinson HM, Pomerance A. The clinical significance of senile cardiac amyloidosis—a prospective clinico-pathological study. *QJ Med* 1977;46:381–7.
16 Gestenblith G, Fredriksen J, Yui FC, Fortuin NJ, Lakatta EG, Weisfeldt MC. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273–8.
17 Kostis J, McCrone K, Moreyra A, Gotzoyannis S, Aglitz N, Natarajan N, *et al*. Premature ventricular complexes in the absence of identifiable heart disease. *Circulation* 1981;63:1351–6.
18 Sandler H, Dodge H. The use of single plant angiocardiograms for the calculation of left ventricular volume in man. *Am Heart J* 1968;75:325–34.
19 Bigger J, Fleiss J, Kleiger R, Miller J, Rolnitzky L, and the Multicentre Post-Infarction Research Group. The relationships among ventricular arrhythmias left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250–8.
20 Greene H, Richardson D, Barker A, Roden D, Capone R, Echt D, Friedman L, Gillespie M, Hallstrom A, Verter J, and the Cardiac Arrhythmia Pilot Study Investigators. Classification of deaths after myocardial infarction as arrhythmic or nonarrhythmic. *Am J Cardiol* 1989;63:1–6.
21 Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: Selection of optimal processing techniques. *Eur Heart J* 1989;10:1060–74.
22 Cripps T, Malik M, Farrell T, Bennett DE, Ward D, Camm AJ. Clinical application of a new method for quantification of heart rate variability in acute myocardial infarction patients: performance in comparison with other prognostic indicators. *Br Heart J* 1991;65:14–19.
23 Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm AJ. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991;68:434–9.
24 Farrell T, Bashir Y, Cripps T, Bennett E, Ward D, Camm AJ. A simple method of risk stratification for arrhythmic events based on heart rate variability and signal-averaged electrocardiogram. *J Am Coll Cardiol* (in press).
25 Vismara L, Amsterdam E, Mason D. Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. *Am J Med* 1975;59:6–11.
26 Daly L, Hickey L, Graan I, Mulcahy R. Predictors of sudden death up to 18 years after a first attack of unstable angina or myocardial infarction. *Br Heart J* 1987;58:567–71.
27 Schulze R, Strauss H, Pit B. Sudden death in the year following myocardial infarction: relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. *Am J Med* 1977;62:192–9.
28 Miyazaki T, Zipes D. Protection against autonomic denervation following acute myocardial infarction by preconditioning ischaemia. *Circ Res* 1989;54:437–48.
29 O'Malley K, Docherty JR, Kelly JB. Adrenoceptor status and cardiovascular function in ageing. *J Hypertens* 1988;6:59–62.
30 Kelly J, O'Malley K. Adrenoceptor function and ageing. *Clin Sci* 1984;66:509–16.
31 Leclercq JF, Maisonblanche P, Cauchemez B, Coumel P. Respective role of sympathetic tone and of cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holster monitoring. *Eur Heart J* 1988;9:1276–83.
32 Stevenson WG, Linssen GC, Havenith MG, Brugada P, Wellens HJ. The spectrum of death after myocardial infarction: A necropsy study. *Am Heart J* 1989;118:1182–8.
33 Gundersen T, Abrahamsen AA, Kjekshus J, Ronnevik PK, for the Norwegian Multicentre Study Group. Timolol-related reduction in mortality and reinfarction in patients aged 65–75 years surviving acute myocardial infarction. *Circulation* 1982;66:1179–84.

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Emergency coronary artery surgery after refractory cardiac arrest: a single centre experience

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Abstract

***Objective*—To determine the incidence and outcome of refractory cardiac arrest necessitating emergency coronary artery bypass grafting.**

***Design*—Retrospective survey of cardiac catheterisation and surgical records.**

***Setting*—The London Chest Hospital.**

***Patients*—All patients requiring emergency coronary artery bypass grafting after cardiovascular collapse in the catheterisation suite between January 1984 and December 1989.**

***Main outcome measures*—Incidence of refractory cardiac arrest in the study group and perioperative mortality.**

***Results*—Thirteen of 8675 patients undergoing coronary arteriography or angioplasty had refractory cardiac arrests. Five patients died, but the remainder survived to be discharged from hospital without serious morbidity.**

***Conclusion*—Without immediate surgical intervention the mortality for these 13 patients would have been 100%.**

Emergency myocardial revascularisation is occasionally required after coronary angioplasty or arteriography. Angioplasty is the higher risk procedure and 1 to 6% of patients will require emergency surgery.[1] Of these, up to one third will present to the surgical team with severe left ventricular dysfunction and cardiogenic shock.[2] Two thirds of patients who undergo acute coronary occlusion will require bypass surgery.[3] Coronry arteriography may also be complicated by coronary artery dissection or occlusion and a recent study reports an incidence of about 0·3% and mortality of 0·2%.[4] There is a high probability that all patients with cardiogenic shock secondary to unsuccessful balloon dilatation develop some myocardial necrosis. The incidence of nonfatal new Q wave myocardial infarction in patients undergoing emergency surgery after failed coronary angioplasty is 25 to 40%.[5-7] The mortality for revascularisation in these cases is also high and previous reports have indicated a high operative mortality in those patients who have cardiac arrest at the time of operation.[8 9] This survey details the results of emergency revascularisation in patients with refractory cardiac arrest during or immediately after coronary arteriography or angioplasty at a single centre.

Patients and methods

A full, retrospective survey of cardiac catheterisation and surgical records for the six year period, January 1984 to December 1989, was undertaken. The incidence of refractory cardiac arrest, which complicated coronary arteriography or angioplasty and necessitated emergency surgery, was found. Refractory cardiac arrest was defined as cardiac arrest unresponsive to conventional treatment including cardiotonic drugs, external cardiac massage, and repeated defibrillation, with resuscitative efforts continued up to median sternotomy, followed by internal cardiac massage. This group did not include complications of valvar disease investigation or postinfarction ventricular rupture. We excluded patients with transient rhythm or haemodynamic disturbances who did not develop refractory cardiac arrest requiring full resuscitation during transfer to the operating theatre. These have been reported elsewhere.

All angioplasty patients had adequate vascular access in the form of femoral venous and arterial cannlas before cardiac arrest. Patients undergoing diagnostic arteriography had only rudimentary access via the brachial arteriotomy and a peripheral venous cannula. During the course of resuscitation, central (jugular) venous access was secured in seven patients.

Cardiopulmonary bypass in this critical situation was carried out as follows in: a member of staff wearing a sterile gown performed external cardiac massage through a betadine soaked swab while preparation and draping proceeded around him. Fully scrubbed and gowned surgeons then continued the massage, which was momentarily interrupted for scalpel incision down to the sternum. After rapid sternotomy, insertion of a chest spreader, and opening of the pericardium (manoeuvres which take seconds), internal cardiac massage was performed by one surgeon, while another inserted cannulation purse strings. Aortic and right atrial cannulas were then inserted with prompt initiation of bypass.

When necessary, a monitoring needle was inserted in the aorta for the adjustment of perfusion pressure and flow after initiation of cardiopulmonary bypass. Most of our patients were operated on using the technique of intermittent ischaemic arrest at 32°C rather than cold cardioplegic arrest.

At the time of the initial cardiac arrest, all

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Table 1 Preoperative and angioplasty/angiography data

Patient	*Age/sex*	*Presentation*	*Site of disease*	*PTCA artery*
1	55 M	UA	RCA/LAD	RCA
2	66 W	UA	LAD/Cx	LAD
3	54 W	SA	RCA/LAD/Cx	LAD/Cx injury
4	62 W	UA	RCA/LAD	RCA/LAD
5	52 W	UA	LAD/Cx	LAD
6	61 M	SA	RCA/LAD	LAD
7	60 W	UA	LAD	LAD/Cx injury
8	72 M	UA	RCA/LAD/Cx	LAD/Cx injury
9	59 M	UA	LAD/Cx	LAD
10	51 M	PIA	LAD/Cx	LAD/Cx injury
11	62 M	SA	LMS/occ RCA	N/A
12	48 W	SA	LMS/RCA	N/A
13	57 W	PIA	RCA/LAD/Cx	N/A

PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; LAD, left anterior descending artery; Cx, circumflex artery; LMS, left main stem; Occ, occluded; N/A, not applicable; PIA, post infarct angina; SA, stable angina; UA, unstable angina.

patients were intubated and ventilated with 100% oxygen. No inhalational anaesthetic agents were administered. Despite the moribund condition of these patients, intravenous anaesthetic drugs, if only a small dose of benzodiazepine with pancuronium, were rarely withheld before sternotomy. Once on cardiopulmonary bypass, the routine opiate benzodiazepine relaxant sequence normally used was given with only minor modifications in dosage.

Heparin, (3 mg/kg) was given at the earliest opportunity bearing in mind the slow circulation time that is inevitable with intermittent cardiac massage. All angioplasty patients had also received 100 mg of heparin at the outset of the procedure.

Various treatments were directed towards preservation of vital organs. These included 10 g mannitol and 2 g methylprednisolone or 20 mg dexamethasone for putative cerebral protection, glyceryl trinitrate infusion to facilitate myocardial preservation, and for renal protection, dopamine infusion and diuretics. Barbiturates were not used at all in either anaesthetic or cerebrally protective doses.

Results

Tables 1 and 2 show the preoperative and perioperative details of the 13 patients. Diagnostic coronary arteriography was performed in 7635 patients at the London Chest Hospital in the study period 1984 to 1989. Eight patients (0·1%) were referred for urgent surgery from the catheter laboratory because of haemodynamic instability or severe myocardial ischaemia. Of these eight patients, three (0·03%) had cardiac arrests requiring full resuscitation including external cardiac massage during transfer to theatre for surgical revascularisation. All three survived and made a good functional recovery, although two had perioperative myocardial infarction on electrocardiographic criteria.

Table 2 Perioperative details and outcome

Patient	*Rhythm*	*Duration of CPR (min)*	*Operation*	*Operative technique*	*Days in ICU*	*Outcome*
1	VF	45	VG × 2	Int fib	2	Survived
2	VF/asystole	45	VG × 2	Int fib	N/A	Died in OT
3	Bradycardia/VF	60	VG × 2	CPL	N/A	Died in OT
4	2:1 AVB/VF	30	VG × 2	CPL	7	Died MSOF
5	VF	30	VG × 2	Int fib	2	Survived
6	VF	40	VG × 2	Int fib	N/A	Died in OT
7	VF	<30	VG × 2	Int fib	2	Survived
8	VF	40	VG × 4	Int fib	6	Survived
9	VF	45	VG × 2	Int fib	N/A	Died in OT
10	VF	<30	VG × 2	Int fib	4	Survived
11	VF	45	VG × 3	Int fib	4	Survived
12	Asystole	30	VG × 3	CPL	4	Survived
13	VF/asystole	30	VG × 3	CPL	3	Survived

CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; AVB, atrioventricular block; VG, vein graft; Int fib, intermittent fibrillation; CPL, cardioplegia; MSOF, multisystem organ failure; N/A, not applicable; OT, operating theatre.

During the same period, 1040 patients underwent percutaneous coronary angioplasty. Sixty seven (6·4%) of these patients were referred for urgent surgery. The reasons for surgical referral included coronary artery dissection and occlusion, persistent chest pain, or ST segment changes despite apparently successful angioplasty, and failure to pass a guidewire or angioplasty catheter across a critical lesion associated with pain and electrocardiographic changes. In 10 patients (1%) immediate surgery was required for refractory cardiac arrest with complete circulatory collapse. The maximum time to cardiopulmonary bypass was 45 minutes. Four patients could not be resuscitated despite rapid surgical intervention and revascularisation, and maximum inotropic support, and died in the operating theatre. One patient died of low cardiac output and multi system organ failure seven days after operation. The mortality for the complication of refractory cardiac arrest after angioplasty was therefore 50%.

The survivors for both groups (61%) had remarkably uncomplicated postoperative courses in the light of their history. One patient (no 5) came off cardiopulmonary bypass with no support at all and was discharged from intensive care the next day. Two patients required inotropic support and four also had assistance from surgically introduced intra-aortic balloon pumps. Six patients were discharged from intensive care by day 3. One remained intubated to day 4 because of a recurrent pneumothorax, and another with a pre-operative history of chronic bronchitis remained in intensive care for six days. Functional recovery was excellent: there was no evidence of cerebral, pulmonary or renal deficit in any of the long-term survivors and their median post-operative hospital stay was 15 days (range 8–30). In two patients, hospital discharge was delayed by superficial infection of an intra-aortic balloon entry site reflecting the less than ideal preparation of patients before surgery. There had been no late deaths at one year follow up.

Discussion

The provision of surgical cover for invasive cardiological diagnostic and therapeutic procedures has been the subject of much debate.[4,10,11] This study, while raising issues that have been discussed previously, throws some light on the problem of identifying what determines the outcome of those patients who have the very worst angiographic complication—refractory cardiac arrest. Stewart *et al* have indicated that it is extremely difficult to prove the assumption that the temporal and geographical availability of surgical facilities affects the prognosis of patients referred for emergency surgery.[4] This difficulty must be all the greater when the patients in question include those with some spontaneous cardiac output who can, albeit precariously, be supported during any delay. In this report, therefore, we have considered in detail only those patients with refractory cardiac arrest as we believe that survival would not have been possible without recourse to immediate surgery which allowed the institution of cardiopulmonary bypass and steps towards reperfusion within an hour of arrest. Our results show that 61% of such patients survived this ultimate of complications with excellent functional recovery after comparatively short stays in intensive care and hospital. We know of no other data from the United Kingdom to suggest that similar patients would achieve a similar outcome if transferred to another hospital.

Whereas it is possible that all our patients would have survived if transferred elsewhere, we believe that a salvage rate of this order is only likely to be achieved if invasive cardiological procedures are performed in the same place as cardiac surgery facilities are available for rapid intervention should refractory cardiac arrest occur. This belief is in accordance with that of other workers.[4] Whether this mortality can be offset by the development of local diagnostic coronary angiographic services saving lives by earlier diagnosis and referral for surgical intervention of prognostically important coronary disease is not known, but has been previously considered.[10 12] Certainly, increased availability of diagnostic procedures will not influence mortality unless treatment facilities expand in parallel.

On site surgical cover for percutaneous transluminal angioplasty has been recommended in American practice,[13] but formal guidelines have not been issued in the United Kingdom. Other workers have suggested that coronary angioplasty can be safely performed at centres distant to surgical facilities and quote considerable and equivalent times to revascularisation with both on site and distant referral.[10] The delay is identified as nonavailability of a cardiac operating theatre.

At the London Chest Hospital there is no special provision for an empty theatre on stand by, but angioplasty procedures have generally been timed to occur when the first surgical cases are nearing completion. This overlapping practice contributes to a reduction in delay should surgical intervention be necessary. Also, it has been accepted that other sites—for example, the catheter laboratory or anaesthetic room—can be used as an operating theatre in desperate circumstances. We have found surgery in the catheter laboratory less than ideal. The risk of transfer and increased delay for patients undergoing external cardiac massage is likely to be offset by the benefits of surgeons, anaesthetists, and support staff operating in a familiar and properly equipped environment.

The problem of speed of access to surgical facilities is likely to be the most decisive factor influencing outcome, but there are other considerations worthy of discussion in the future. These include catheter laboratory techniques,[4] the skill and seniority of the cardiologist, the speed of recognition of a serious problem, and the initial resuscitation efforts with early involvement of anaesthetists and surgeons of adequate seniority. It is not our view or experience that failure to establish a rhythm and cardiac output makes revascularisation pointless.

Our method of establishing cardiopulmonary bypass was always by direct central cannulation following sternotomy. Percutaneous femoral cannulation kits were not available to our unit, and we considered that to try to isolate, control, and tape the femoral vessels, and insert the femoral cannulas, with the patient undergoing external cardiac massage, was time consuming and difficult. Appropriate coordination of personnel to continue ventilation and external cardiac massage during preparation and draping allowed prompt sternotomy and completion of cardiopulmonary bypass. More peripheral manoeuvres, although suitable in some centres, would have led to a delay of revascularisation in our practice.

In conclusion, this study shows that significant surgical salvage rates can be achieved by prompt intervention in this extremely high risk subgroup of patients. Centres that undertake invasive cardiology will have a complication rate that includes refractory cardiac arrest, an event that is unpredictable. Our results show that, in this event, a 61% survival rate is achievable and therefore we argue strongly that cardiological and surgical facilities should be close.

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1 Cowley MJ, Dorros G, Kelsey SF, Raden MV, Detre KM. emergency coronary bypass surgery after coronary angioplasty: the National Heart, Lung, and Blood Institute's percutaneous transluminal angioplasty registry experience. *Am J Cardiol* 1984;53 (suppl):22–6.

2 Bolooki H. Emergency cardiac procedures in patients in cardiogenic shock due to complications of coronary artery disease. *Circulation* 1989;79 (suppl I):137–48.

3 King SB III. Prediction of acute closure in percutaneous transluminal coronary angioplasty. *Circulation* 1990;81: 5–7.

4 Stewart JT, Gray HH, Ward DE, Pumphrey W, Redwood DR, Parker DJ. Major complications of coronary arteriography: the place of cardiac surgery. *Br Heart J* 1990;63:74–7.

5 Spencer FC. A critique of emergency and urgent operations for complications of coronary artery disease. *Circulation* 1989;79 (suppl I):160–2.

6 Talley JD, Weintraub WS, Anderson HV, *et al.* Late clinical outcome of coronary bypass surgery after failed elective PTCA [abstract]. *Circulation* 1987;76 (suppl IV):352.

7 Ullyot DJ. Surgical standby for percutaneous coronary angioplasty. *Circulation* 1987;76 (suppl III):149–52.

8 Golding LAR, Loop FD, Hollman JL, *et al.* Early results of emergency after coronary angioplasty. *Circulation* 1986; 74: (suppl III):26.

9 Reul GJ, Cooley DA, Hallman GL, *et al.* Coronary artery bypass for unsuccessful percutaneous transluminal coronary angioplasty. *J Thorac Cardiovasc Surg* 1984;88: 685–94.

10 Richardson SG, Morton P, Murtagh JG, O'Keeffe DB, Murphy P, Scott ME. Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty: experience of complications in a hospital without on site facilities for cardiac surgery. *Br Med J* 1990;300:355–8.

11 Bayliss J, Shakespeare C, Lincoln C, Sutton R. Does invasive cardiology require the presence of surgery? [abstract] *Br Heart J* 1987;57:79.

12 Mills P. Should coronary angiography be performed in district hospitals? *Br Heart J* 1990;63:73.

13 Ryan TJ, Faxon DP, Gunnar RM, *et al.* Guidelines for percutaneous transluminal coronary angioplasty. *Circulation* 1988;2:486–502.

Br Heart J 1992;67:395–401

Predictors of risk in patients with unstable angina admitted to a district general hospital

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Abstract

***Objective*—To observe the long-term prognosis of patients with unstable angina and select simple criteria to identify high and low risk subgroups.**

***Design*—A six month prospective survey with three year follow up.**

***Setting*—One eleven bed coronary care unit.**

***Patients*—All patients admitted with chest pain in whom no infarct was confirmed by subsequent electrocardiographic or enzyme changes and for whom no alternative cause of chest pain was found were studied. Unstable angina was also diagnosed if there was evidence of myocardial ischaemia in the form of previous effort angina, previous myocardial infarction, or if transient electrocardiographic changes accompanied the pain. When none of the above were present, chest pain without a known cause, was diagnosed.**

***Interventions*—No routine intervention. Angiography and revascularisation for persistent symptoms despite medical treatment.**

***Outcome measures*—Death or non-fatal infarction.**

***Results*—In the 141 patients with unstable angina there were eight deaths and five non-fatal infarctions during the first eight weeks. Symptoms of increasing angina before admission were similar in all three groups and did not help predict early complications. Recurrence of pain in hospital, a rise in cardiac enzymes to less than twice the upper limit of normal, and transient electrocardiographic changes were all associated with an increased risk of early events. The presence of either abnormal enzyme activity or more than five episodes of pain in hospital identified a group of 49 in whom 11 of the 13 early events occurred. After three years, 29 of the 141 patients had died and eight had had infarctions (overall event rate 26%). Seventeen had undergone revascularisation (12%) and 51 (36%) were on antianginal treatment. Thirty six (26%) were still alive, without new myocardial infarction, and were free of angina. In the 29 patients with chest pain without a known cause there were no early events and only one non-fatal infarction during the three year follow up.**

***Conclusion*—When patients are admitted to the coronary care unit with chest pain not due to myocardial infarction, the history, electrocardiography and measurement of cardiac enzymes are sufficient to identify high and low risk subgroups.**

Cardiologists in regional centres tend to see unstable angina as an emergency situation requiring angiography and intervention, even though there is little evidence that such action improves prognosis. The perspective from a district general hospital is, however, completely different. For more than half the patients admitted with suspected myocardial infarction the diagnosis is not confirmed and many of these patients could by some definitions be diagnosed as having unstable angina. These patients usually require only a very brief stay in hospital, and there are no immediate clinical problems in most of them. Emergency referral to a regional centre because of persistent angina when at rest is a rare event.

In 1986, after Cairns *et al* had confirmed the benefit of aspirin in unstable angina,[1] a finding previously reported in the Veterans' Administration study,[2] we prospectively followed up all patients admitted to our coronary care unit in a six month period with the aim of finding the proportion of patients who could be considered to have unstable angina, and of identifying high and low risk subgroups. We wanted to see how many of these patients progressed over a fairly long period, and we aimed to collect data that would be useful for the design of later trials. A subsidiary intention was to see how quickly aspirin would become part of routine clinical treatment in a unit where patients are looked after by general physicians on emergency intake.

The subgroups defined by Conti *et al*—namely angina of recent onset, angina of increasing severity, and angina at rest—are clearly not of great value to patients in hospital, almost all of whom will have had persistent pain when at rest.[3] We therefore set out with no preconceived definition of unstable angina, but identified patients who needed admission because of suspected ischaemic chest pain but who were found not to have had a myocardial infarction.

Patients and Methods

Between 1 January and 30 June 1986 all admissions to the coronary care unit at University Hospital, Nottingham, were studied. The 11 bed unit receives patients in the care of four

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general medical firms, one of which has an interest in cardiology. While in hospital, patients remain under the control of the admitting medical firm who determine management.

University Hospital shares with Nottingham City Hospital a catchment population of roughly 650,000. Referrals from general practice are divided between the two hospitals and University Hospital also receives all admissions from Nottingham's only accident and emergency (A and E) department. It is our policy that whenever possible, patients with suspected myocardial infarction are admitted to the coronary care unit, although this sometimes depends upon the availability of beds and the relative clinical needs of individual patients. The number of patients admitted to medical or geriatric wards with suspected infarction (all patients in whom cardiac enzymes were measured) was obtained from the Nottingham Heart Attack Register (Gray D, personal communication).

Patients admitted to the coronary care unit were interviewed by questionnaire within 24 hours of arrival, except in the case of early death or self discharge when information was obtained from the admission notes. Details of the presenting complaint and cardiac history were recorded. A modified Rose questionnaire was used to identify angina after effort and any change in symptoms within the previous four weeks was noted.[4] Angina was considered to be more frequent if it occurred at least twice as often as before and changes in the character of the pain were also recorded. In all cases, cardiac enzymes (aspartate aminotransferase and hydroxybutyrate dehydrogenase) and standard 12 lead electrocardiograms were recorded over three consecutive days, other investigations being performed at the discretion of the individual medical firms.

Patients with chest pain or tightness of at least 15 minutes duration in the 48 hours preceding admission were allocated to one of five diagnostic groups after the results of cardiac enzyme activity measurement and electrocardiograms. When cardiac pain was due to a primary cause other than coronary artery disease, such as an arrhythmia, cardiomyopathy, or valve disease, secondary angina was diagnosed.

The diagnosis of acute myocardial infarction was made when two of three criteria were fulfilled: (*a*) chest pain for at least 15 minutes; (*b*) increase in at least one cardiac enzyme above twice the upper limit of normal in the absence of an obvious non-cardiac cause, and (*c*) new electrocardiographic changes characteristic of infarction; these were pathological Q waves (at least 40 ms duration and 1/3 of the R wave height) in two adjacent leads, a dominant R wave in V1 and V2 (> 1 mm and larger than the S wave), a new bundle branch block or ST-T wave changes persisting for more than three days (non-Q wave infarction). Patients with electrocardiographic changes lasting less than 72 hours who did not have a diagnostic enzyme rise were labelled as unstable angina, as described later. The acute myocardial infarction group also included patients presenting with breathlessness, collapse, or arrhythmia without chest pain, in whom both electrocardiographic and enzyme criteria were filfilled.

When, in the opinion of the attending medical firm, features of the history, examination, or subsequent investigations were sufficient to make a specific non-cardiac diagnosis then non-cardiac pain was diagnosed.

After the exclusion of infarction, the label of unstable angina was given if the admission symptoms were supported by evidence of ischaemic heart disease in the form of (*a*) effort related angina as defined by the Rose questionnaire in the preceding four weeks; (*b*) a documented previous infarction (using the criteria given previously); or (*c*) ST-T wave changes in association with pain lasting less than 72 hours.

Three subgroups of unstable angina were selected in advance as they were considered to represent levels of increasing probability that the presenting symptoms reflected myocardial ischaemia. Patients in group 1 had a history of effort related angina but had had no evidence of previous infarction and no electrocardiographic changes with the presenting pain. Patients in group 2 had had a previous infarction but had no new changes on the electrocardiogram. Group 3 contained patients with ST-T wave changes in association with the admission pain but which persisted for less than 72 hours and who did not have a rise in enzyme activity diagnostic of infarction. Some of the patients in group 3 had also suffered a previous infarction and a proportion of patients in groups 2 and 3 had already had effort related angina.

The remaining patients were diagnosed as having chest pain without a known cause. This group had no history of angina or infarction, normal electrocardiograms and cardiac enzymes, and no features to support a non-cardiac diagnosis. Within two weeks of admission these patients underwent a symptom limiting treadmill exercise test according to the Bruce protocol. A positive result was defined as chest pain in association with 1 mm horizontal or downsloping ST segment depression, measured at 80 ms after the J point, or 2 mm of ST segment depression without pain.

With the exception of non-cardiac pain the above diagnostic labels were independent of the attending physicians. For the purposes of the study, patients in whom acute myocardial infarction was diagnosed were only followed up until discharge from hospital. All patients in the three subgroups of unstable angina and those with chest pain without a known cause were followed up for at least three years after discharge for the development of cardiac events. This follow up was independent of the physicians involved with management. During the three year period, myocardial infarction was diagnosed by the criteria as already described and cause of death was ascertained from death certificates, supported by a review of hospital and general practice notes. After three years a second Rose questionnaire was used to examine the prevalence of effort related angina in all survivors.

STATISTICAL ANALYSIS

Survival curves were constructed for cardiac death and non-fatal infarction combined. The Lee-Desu method was used for statistical comparisons. Contingency tables were analysed by χ^2 test and parametric data by analysis of variance with logarithmic transformation as necessary.

Results

ALL CORONARY CARE UNIT ADMISSIONS

Over the six month study period there were 809 admissions to the coronary care unit, 530 of which were either associated with chest pain, or acute myocardial infarction was suspected for other reasons. Information about 10 patients was collected solely from the case records and the remainder were interviewed within 24 hours. Acute myocardial infarction was the final diagnosis in 304 admissions (285 patients), unstable angina in 149 admissions (141 patients), and chest pain without a known cause in 31 (29 patients). In 32 patients admitted with pain due to cardiac ischaemia, a primary cause other than coronary artery disease was diagnosed, such as aortic stenosis, an arrhythmia, or severe anaemia. Non-cardiac pain was the diagnosis in the remaining 14; there were six patients with chest infection and pleurisy, two with pulmonary embolism, three with oesophagitis, and one each with aortic dissection, pancreatitis, and thoracic root pain. Table 1 shows the characteristics and in hospital clinical course of patients with myocardial infarction, unstable angina, and chest pain without a known cause.

Table 1 Characteristics and in hospital outcome of consecutive patients admitted to the coronary care unit according to final diagnosis

No of admissions	*AMI (n=304)*	*Unstable angina (n=149)*	*CP?C (n=31)*
Age (y, mean (range))	60 (32–83)	58 (33–82)	49 (35–74)*
% Men	232 (76)	112 (75)	24 (77)
Smokers (%)	223 (66)	75 (50)	20 (69)
Pain for >30 min (%)	294 (97)	120 (80)	22 (80)*
Previous AMI (%)	78 (26)	80 (54)	—*
CCU, stay in days (mean (range))	2·3 (1–14)	1·3 (1–4)	1·1 (1–2)*
Hospital stay in days (mean (range))	8 (1–56)	5 (1–26)	3 (1–8)*
Death (%)	39 (13)	3 (2)	0

AMI, acute myocardial infarction, CP?C, chest pain without a known cause; CCU, coronary care unit.
*Analysis of variance, $p < 0{\cdot}01$.

Table 2 Pre-admission characteristics of the three groups with unstable angina

	Angina only (n=35)	*Previous AMI (n=39)*	*ST-T changes (n=67)*
Age (y, mean (range))	56 (34–82)	59 (44–77)	59 (33–76)
% Men	23 (66)	31 (79)	50 (75)
Smoker (%)	11 (31)	18 (46)	35 (52)
Previous AMI (%)	0	39 (100)	38 (57)

AMI, acute myocardial infarction.

Table 3 The frequency and change of angina symptoms over the preceding four weeks in the three unstable angina groups

	Angina only (n=35) No (%)	*Previous AMI (n=39) No (%)*	*ST-T changes (n=67) No (%)*
Effort related angina	35 (100)	24 (61)	35 (52)
Onset in previous four weeks	2 (6)	2 (6)	5 (7)
Pain at rest	20 (57)	28 (72)	47 (70)
Doubled angina frequency	13 (37)	17 (44)	31 (46)
Restricting activity	17 (49)	18 (46)	30 (45)
More intense pain	15 (43)	16 (41)	29 (43)
Longer episodes	13 (37)	16 (41)	36 (52)
More GTN use	11 (31)	10 (26)	18 (27)

GTN, glyceryl trinitrate; AMI, acute myocardial infarction.

During the same period, 356 patients in whom cardiac enzymes were measured were admitted to medical wards, rather than to coronary care. These patients were not followed up for the purposes of this study, but in general they tended to be older and the range of final diagnoses was much wider. There were 73 deaths in hospital within this group.

Twenty four of the 29 patients with chest pain without a known cause underwent exercise testing and there was only one positive result. This patient developed 2 mm ST segment depression in leads V4–V5 during stage IV of the Bruce protocol that was not associated with chest pain; she remained pain free and event free for the whole of the three year follow up. The five patients who did not undergo an exercise test were unable or unwilling to walk on the treadmill. Over three years, within the whole group, there was only one cardiac event, a non-fatal infarction. This patient had undergone exercise testing after his index admission, during which he had reached stage V without chest pain or electrocardiographic changes and he had a normal blood pressure response. After three years, three of the remaining 27 had angina as indicated by a positive Rose questionnaire.

PATIENTS WITH UNSTABLE ANGINA

Eight of the patients with unstable angina were admitted twice during the six month study period, but survival data were only analysed for the first admission. One hundred and forty one patients with unstable angina therefore formed the basis of this study. These patients were divided into the three groups defined above: 35 patients gave a history of effort related angina as defined by a positive Rose questionnaire, but had no electrocardiographic abnormalities at any time (group 1), 39 patients had a documented previous myocardial infarction, but no new electrocardiographic changes (group 2), and in 67 there were transient ST-T wave changes accompanying pain (group 3). Thirty eight patients in group 3 had had a previous myocardial infarction as well as transient ischaemic changes.

Pre-admission characteristics

Table 2 shows the age, sex, smoking habit, and frequency of previous myocardial infarction in the three groups of patients with unstable angina. Table 3 shows the characteristics of the anginal pain of these patients during the four weeks before admission. Symptoms of worsening angina were equally common in the three groups, and no featues in the history served to distinguish them.

Early complications

There were three deaths in hospital in the unstable angina group (at days 7, 9, and 24), each resulting from myocardial infarction and giving a mortality of 2% in hospital. The

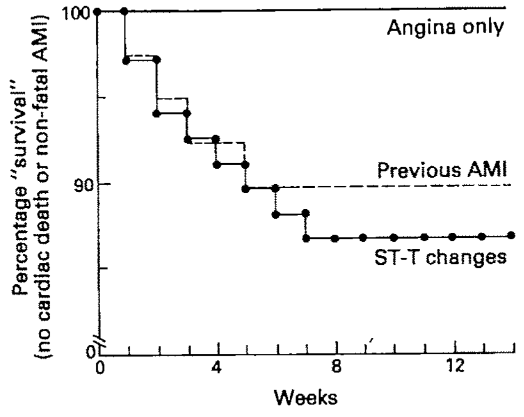

Figure 1 Event free "survival" curves (no cardiac death or non-fatal infarction for patients in the three unstable angina groups. The survival curves of patients with previous acute myocardial infarction (AMI) or acute ST-T changes did not differ and no events occurred in the group with effort related angina only ($p < 0.001$).

remaining patients were considered to have settled on medical treatment so none underwent immediate angiography. Figure 1 shows the event free survival curves for all the patients (including the early deaths) in the three diagnostic categories of unstable angina. In group 1 there were no cases of myocardial infarction or cardiac death during the first four months. In groups 2 and 3 cardiac events occurred at a constant rate for up to eight weeks after admission, so this can be regarded as the period of acute instability, which we selected for the study of early events. During this eight week period eight deaths and five non-fatal infarctions occurred in the 141 patients with unstable angina (event rate 9%). There were three deaths with one non-fatal infarction in the 39 patients in group 2 (event rate 10%) and five deaths with four non-fatal infarctions in the 67 patients in group 3 (event rate 13%).

Data relating to the pre-admission and in hospital course of all the patients with unstable angina were reviewed in an attempt to identify factors that might select patients at high risk of developing an early cardiac event. After a review of previous studies[2 5-15] the factors selected were age, the duration of preceding angina, change in symptoms before admission, heart failure (the need for 40 mg/day or more of frusemide), the presence of electrocardiographic abnormalities, direction and site of ST segment shift, and recurrence of pain in hospital. We also examined the influence of rises in minor enzyme levels not diagnostic of infarction.

Those with and without an early event were of comparable mean age (57 *v* 59 years) and most were men (10(77%) *v* 71(76%)). Nine (69%) of the 13 with an early cardiac event had a documented previous infarction compared with 68 (73%) of the remainder. The nature and duration of symptoms of angina before hospital admission were similar in the two groups (table 4) as was the frequency of diuretic use (overall frequency 34%). The site of ST segment or T wave changes (inferior, anterior, or lateral) in group 3 had no influence on the development of subsequent events. As there were only six patients with ST segment elevation, numbers were insufficient to compare those with ST segment elevation and depression. Sub-dividing group 3 (patients with transient electrocardiographic changes) into those with and without a previous myocardial infarction did not identify a high risk group, as there were six events (16%) among the 38 patients with a previous infarction compared with three (10%) among the 30 who had had no previous infarction.

Table 4 The frequency and change of angina symptoms over the preceding four weeks in patients with unstable angina, and a documented previous infarction or transient ECG changes, according to whether or not they developed cardiac death or non-fatal infarction over the next eight weeks

	Death or AMI (n=13) No (%)	*None (n=93) No (%)*
Effort related angina	8 (62)	51 (56)
Onset in previous four weeks	1 (8)	6 (6)
Pain at rest	7 (54)	68 (73)
Doubled angina frequency	7 (54)	41 (44)
Restricting activity	6 (46)	42 (45)
More intense pain	6 (46)	39 (42)
Longer episodes	7 (46)	45 (48)
More GTN use	4 (31)	24 (26)

No differences achieved statistical significance. AMI, acute myocardial infarction.

Recurrence of pain in hospital, defined as a need for treatment with glyceryl trinitrate or opiates, did to some extent predict patients at increased risk. Among the 106 patients in groups 2 and 3, 51 had no recurrence of pain after admission and within this subgroup there were five (11%) who had an early myocardial infarction or cardiac death. There were four (11%) events in the 37 patients who had up to five episodes of recurrent pain and four (22%) events in the 18 patients who had more than five episodes of pain during their admission.

Three features were recognised as helping to identify patients at increased risk of early cardiac events: recurrent pain, reversible electrocardiographic changes, and a rise in cardiac enzymes to less than twice the upper limit of normal. Eight of the 13 early events occurred in 35 patients with minor enzyme rises (sensitivity 62%, specificity 71%, positive predictive accuracy 23%). The presence of reversible electrocardiographic changes identified 67 patients in whom nine early events occurred (sensitivity 69%, specificity 38%, and positive predictive accuracy 13%). Any recurrence of pain was associated with eight events in 55 patients (sensitivity 62%, specificity 49%, positive predictive accuracy 15%). Selecting patients with more than five attacks of pain in hospital identified 18 patients in whom four events occurred (sensitivity 31%, specificity 85%, positive predictive accuracy 22%).

Table 5 shows the value of choosing either of two features as a means of predicting patients at risk of death or myocardial infarction over the subsequent eight weeks. Any recurrence of pain in hospital with either reversible electrocardiographic changes or a minor enzyme rise gave a sensitivity of 92% but the specificity was poor. The selection of patients with either a minor enzyme rise or more than five attacks of pain in hospital gave a slightly lower sensitivity but greatly improved specificity.

Treatment given

Patients with chest pain without a known cause were usually given no treatment once the initial pain had settled, and those with only a history of angina (group 1) were discharged on antianginal treatment as considered appropriate by the attending firm. Forty nine (46%) of the 106

Table 5 Sensitivity, specificity, and positive predictive accuracy when transient electrocardiographic changes (ST-T), recurrence of pain, and minor enzyme rise are combined to identify patients at risk of early cardiac events (n=106)

	No Selected	*Events*	*Sensitivity (%)*	*Specificity (%)*	*Predictive accuracy (%)*
ST-T or any further pain	100	12	92	5	12
ST-T or >5 attacks	74	11	85	33	15
ST-T or minor enzyme rise	80	10	77	25	12·5
Minor enzyme rise or >5 attacks	54	11	85	54	20
Minor enzymes or any further pain	88	12	92	18	14

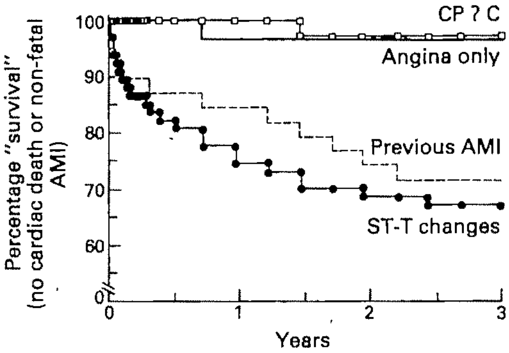

Figure 2 Long term event free "survival" curves for patients with chest pain without a known cause (CP?C) and the three unstable angina groups. Patients with angina only (group 1) and CP?C had a similar prognosis. The survival curves for patients with previous acute myocardial infarction (AMI) or reversible ST-T changes (groups 2 and 3) did not differ but were both significantly worse than group 1 and CP?C (p < 0·001).

patients with a previous myocardial infarction or with transient electrocardiographic changes (groups 2 and 3) were treated with β blockers, 27 (25%) with calcium antagonists, and 49 (46%) with long acting nitrates. Twelve patients were given three anti-anginal drugs (one from each therapeutic class), 24 were given two, and 41 were given monotherapy. Twenty nine patients were given no angina prophylaxis although most received sublingual nitrates. Only one patients was treated with aspirin and none received thrombolytic therapy or intravenous heparin. The treatment given did not appear to influence the subsequent development of serious cardiac events.

During the eight weeks after discharge, two of the 35 patients with angina only (group 1) had coronary artery bypass graft surgery, as did three of the 67 patients with transient electrocardiographic changes (group 3). In each case the operation was performed because of persistent angina despite maximum medical therapy. No patient in group 2 was considered to need surgery during the first eight weeks. No patients were treated by percutaneous transluminal angioplasty.

Three year follow up

Figure 2 shows the long term event free survival curves for the patients with chest pain without a known cause and for those in the three different categories of unstable angina. Table 6 separates the different types of cardiovascular event, and shows the morbidity among the different groups. Patiens in group 1 (angina only) had a similar survival pattern to patients with chest pain without a known cause. After three years, 16 (46%) of those who had been admitted with angina still had this complaint, but 13 (37%) were completely free both of events and angina.

Table 6 The state of patients in the unstable angina groups three years after admission

	Angina only (n=35) No (%)	*Previous AMI (n=39) No (%)*	*ST-T changes (n=67) No (%)*
Cardiac death	—	9 (23)	18 (27)
Non-cardiac death	1 (3)		1 (1)
Non-fatal AMI	1 (3)	3 (8)	4 (6)
CABG or angioplasty	4 (11)	7 (18)	6 (9)
Angina on medical treatment	16 (46)	12 (31)	23 (34)
No angina, events, or surgery	13 (37)	8 (21)	15 (22)

CABG, coronary artery bypass grafting; AMI, acute myocardial infarction.

In groups 2 and 3, the initial high event rate in the first two months decreased, but events continued to occur over the whole three year peiod. Only eight (21%) of the 39 patients who had had a previous infarction (group 2) and 15 (22%) of the 67 patients with reversible ST-T changes (group 3) remained free of symptoms and events after three years. The groups with continued complications tended to be older (mean of 61 *v* 58 years) although this did not achieve statistical significance (p = 0·11).

Discussion

Acute coronary insufficiency was described by Master *et al* in 1947 as a condition in which the pattern of angina changed abruptly and which was associated with episodes of pain lasting 30 minutes or more.[16] In 1961 Wood reported 150 cases and found that myocardial infarction occurred within two months in 22%; he believed that anticoagulation reduced this dramatically.[17] Since then the condition now usually called unstable angina[3] has received many names, including the intermittent coronary syndrome, acute myocardial ischaemia, pre-infarction angina, impending myocardial infarction, status anginosus, and accelerated angina.[18] All these names seem to imply a dangerous and changing state, about which something must be done.

After trials with thrombolytic agents, aspirin, β blockers, calcium antagonists, and percutaneous transluminal coronary angioplasty (PTCA) the management of patients with acute myocardial infarction has become increasingly well defined, but unstable angina still presents a major problem. Apart from aspirin[1 2] and ticlopidine[19] (which is not available in the United Kingdom), there is no clear evidence on which to base a management policy for such patients, although an overview of β blocker trials[20] and recent studies of heparin suggest benefit.[21 22] A contemporary review recommends aspirin or heparin in combination with a β blocker as the first therapeutic option, a calcium antagonist being added if symptoms persist.[23] For those with recurrent angina, angiography and revascularisation are logical progressions but are not without risk and their effect on the natural history is unknown.[24 25] In a study in the 1970s that compared early surgery with medical treatment there was little difference in mortality,[26] but the surgical group had a higher rate of early infarction whereas the medical group had a higher rate of late angina, eventually leading to surgery. Although these data are generally interpreted as recommending caution against early intervention, some enthusiasts still recommend angiography and some form of revascularisation for all patients with unstable angina.[27]

Comparisons between the cardiovascular event rates which we found and other published data are difficult because of differences with case selection, and because different durations of follow up have been described. In a community study of patients, not in hospital, with recent onset or worsening of pre-existing angina, the one month and six month cardiac event rates (fatal and non-fatal infarction combined) were 7% and 13%.[14 28] In studies of patients with unstable angina who were admitted to hospital, the rate of fatalities in hospital varied between 1 and 8%, whereas the one year fatality rate was 10–18%. The event rate one month after admission was between 9 and 13%.[8 9 11 15]

Control groups from trials of drug treatments give a clearer view of the importance of case selection. In the Canadian study of aspirin and sulphinpyrazone, patients were included if they had a positive Rose questionnaire or transient electrocardiographic changes with pain.[1] After a mean of 18 months, the event rate in the placebo group was 17% with 11·7% deaths. In the Veterans' Administration study of aspirin, entry to the study depended mainly on the patients' history with some more definitive evidence of underlying coronary disease.[2] The event rate at three months was 10·1% with 3·3% deaths. In the ticlopidine study, which included patients with an appropriate history and transient electrocardiographic changes, the event rate at six months in the control group was 13·6% with 4·7% deaths.[19] These results can be compared with our rate of event at two months of 9% of all patients with unstable angina, 10% in those with a previous infarction, and 13% in those with transient electrocardiographic changes. The relatively low event rate in the Veterans' Administration trial probably reflects the inclusion of cases we have identified as low risk,[2] whereas the patients admitted to the ticlopidine trial were comparable with our high risk group.

Our findings suggest that once two months have elapsed the risk diminishes and is probably similar to that of patients who have survived a myocardial infarction for a similar time. The three year mortality of 25% in our groups 2 and 3 compares with 33% in infarct survivors reported by Norris *et al*.[29] Our early event rate within the first two months in these groups should also be compared with those shown to have had a myocardial infarction. In second international study of infarct survival (ISIS-2),[30] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico (GISSI),[31] and Anglo-Scandinavian study of early thrombosis (ASSET)[32] mortality in the placebo group at one month ranged from 9·8% to 13%; the proportion eventually shown to have a myocardial infarction being variable. At six months 13·1% of the placebo group in ASSET had died (17·1% of those with a definite infarction); at one year 18% of the placebo group in ISIS 2 and 19% of those in GISSI had died. In all of these studies the non-fatal reinfarction rate was low at 3 or 4% in the first month, and up to 6 or 7% in the first six months. Our hospital death mortality rate of 13% for patients with acute infarction is therefore what would have been expected in the pre-thrombolytic era, and this event rate should be compared with the hospital mortality rate of 3%, a mortality rate at two months of 7·5%, and the three year mortality rate of 25% for the 106 patients in groups 2 and 3. In these patients the non-fatal reinfarction rate was 5% at two months.

If we include patients who are admitted to a coronary care unit because of a history suggestive of prolonged ischaemia at rest but who have no other evidence of coronary disease, (chest pain without a known cause group), the outlook is clearly better than it is for patients with myocardial infarction. Patients with only a positive Rose questionnaire as a means of making the diagnosis (our group 1) also have an excellent prognosis so there are high and low risk groups within the overall category of unstable angina. Severi *et al* found,[33] as we did, that patients in whom the diagnosis was made simply on the basis of history had an excellent prognosis, and they showed that the subsequent positive exercise test had little relation to the outcome. Heart failure (defined as an increased cardiothoracic ratio[10 14] or raised left ventricular end diastolic pressure[5]) identified a higher risk group in some but not all studies.[8] Recurrence of pain[8–11 15] and electrocardiographic changes[2 10 12 13 17] have generally been found to identify high risk subgroups, and some authors have also highlighted specific changes on the electrocardiogram. De Servi *et al*[5] found a higher mortality in patients with ST segment depression than with elevation and Sclarovsky *et al*[34] highlighted the significance of T wave changes in those with anterior lead horizontal or downsloping ST segment depression.[6] Left main stem occlusion was present in seven out of 10 of those with T wave inversion and in none of the 21 with upright T waves.[35] In the study by de Zwaan *et al*[7] abnormal ST segments with T wave inversion in V2 and V3 identified patients with a left anterior descending lesion, 83% of whom had the culprit lesion proximal to the first septal perforator. Both a long history of ischaemic heart disease[8] and the lack of preceding symptoms[9 11] have been suggested as identifying high risk subgroups. Our identification of high risk groups was based simply on history, electrocardiogram, and cardiac enzyme activity results—all of which are routinely collected on coronary care unit admissions—so clearly this is a practical way for physicians in district general hospitals to recognise the high risk patient. But should such patients undergo angiography and revascularisation?

Very few events occur in the low risk groups so it seems reasonable to suppose that the beneficial effects of aspirin must depend on a reduced rate of event in what we have called high risk patients. We could therefore assume that treatment with aspirin could have reduced the event rate at two months in this group to perhaps 10%. A clinical trial of any further intervention designed to show, with conventional levels of power and significance (α = 0·05, 1-β = 0·90), a further 30% reduction in events would need to contain 5600 such patients. Assembly of such a trial would, from our experience, require the screening of over 80 000 coronary care admissions. It is clearly going to be extremely difficult to establish whether coronary angiography, percutaneous transluminal coronary angioplasty, or coronary artery bypass will reduce the risk of cardiac death or non-fatal infarction in these patients. The morbidity of the condition is substantial, with only a minority of patients remaining event free and free from angina at three years, so a study that included chronic angina as an undesirable outcome would be more feasible.

We thank Dr D Gray for providing data from the Nottingham Heart Attack register and the physicians of University Hospital, Nottingham for permission to study their patients.

1 Cairns JA, Gent M, Singer J, *et al*. Aspirin, sulphinpyrazone, or both in unstable angina. *N Engl J Med* 1985; 313:1369–75.

2 Lewis HD Jr, Davis JW, Archibald DG, *et al*. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative study. *N Engl J Med* 1983; 309:396–401.

3 Conti CR, Brawley RK, Griffith LS, *et al*. Unstable angina pectoris: morbidity and mortality in 57 consecutive patients evaluated angiographically. *Am J Cardiol* 1973;32:745–50.

4 Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;27:645–58.

5 De Servi S, Ghio S, Ferrario M, *et al*. Clinical and angiographic findings in angina at rest. *Am Heart J* 1986;111: 6–11.

6 Sclarovsky S, Davidson E, Strasberg B, *et al*. Unstable angina: the significance of ST segment elevation or depression in patients without evidence of increased myocardial oxygen demand. *Am Heart J* 1986;112:463–7.

7 De Zwaan C, Bar FW, Janssen JHA, *et al*. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989; 117:657–65.

8 Krauss KR, Hutter AM, De Sanctis RW. Acute coronary insufficiency. Course and follow-up. *Arch Intern Med* 1972;129:808–13.

9 Heng M-K, Norris RM, Singh BN, Partridge JB. Prognosis in unstable angina. *Br Heart J* 1976;38:921–5.

10 Olson HG, Lyons KP, Aronow WS, Stinson PJ, Kuperus J, Waters HJ. The high-risk angina patient. Identification by clinical features, hospital course, electrocardiography and Technetium-99m stannous pyrophosphate scintigraphy. *Circulation* 1981;64:674–84.

11 Mulcahy R, Daly L, Graham I, *et al*. Unstable angina: natural history and determinants of prognosis. *Am J Cardiol* 1981;48:525–8.

12 Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anotomy and hospital outcome. *J Am Coll Cardiol* 1989;13:1495–1502.

13 Madsen JK, Thomsen BL, Mellemgaard K, Hansen JF. Independent prognostic risk factors for patients referred because of suspected acute myocardial infarction without confirmed diagnosis. Prognosis after discharge in relation to medical history and non-invasive investigations. *Eur Heart J* 1988;9:610–8.

14 Duncan B, Fulton M, Morrison SL, *et al*. Prognosis of new and worsening angina pectoris. *BMJ* 1976;1:981–5.

15 Gazes PC, Mobly EM, Faris HM Jr, Duncan RC, Humphries GB. Pre-infarction (unstable) angina—a prospective study—ten year follow-up. *Circulation* 1973; 48:331–7.

16 Master AM, Dack S, Grishman A, Field LE, Horn H. Acute coronary insufficiency: an entity. Shock haemorrhage and pulmonary embolism as factors in its production. *Journal of the Mount Sinai Hospital* 1947;14:8–23.

17 Wood P. Acute and subacute coronary insufficiency. *BMJ* 1961;1:1779–82.

18 Anonymous. Intermittent coronary syndrome. *BMJ* 1973; 3:601–2.

19 Balsano F, Rizzon P, Violi F, *et al*. Antiplatelet treatment with ticlopidine in unstable angina. *Circulation* 1990; 82:17–26.

20 Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;260:2259–63.

21 Theroux P, Ouimet H, McCans J, *et al*. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; 319:1105–11.

22 Serneri GN, Gensini GF, Poggesi L, *et al*. Effect of heparin, aspirin, or alteplase in reduction of myocardial ischaemia in refractory unstable angina. *Lancet* 1990;i:615–8.

23 Lubsen J. Medical management of unstable angina: what have we learnt from the randomized trials? *Circulation* 1990;82 (suppl II):1182–7.

24 Naunheim KS, Fiore AC, Arango DC, *et al*. Coronary artery bypass grafting for unstable angina: risk analysis. *Ann Thorac Surg* 1989;47:569–74.

25 de Feyter PJ. Coronary angioplasty for unstable angina. *Am Heart J* 1989;118:860–8.

26 Russell RO Jr, Rackley CE, Kouchoukos NT. Unstable angina pectoris: do we know the best management? *Am J Cardiol* 1981;48:590–1.

27 Rahimtoola SH. Coronary bypasss surgery for unstable angina. *Circulation* 1984;69:842–8.

28 Fulton M, Lutz W, Donald KW, *et al*. Natural history of unstable angina. *Lancet* 1972;i:860–5.

29 Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. *Lancet* 1970;ii:485–8.

30 ISIS-2 (Second International Study of Infarct Survival) Collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;ii:349–60.

31 Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987;ii:871–4.

32 Wilcox RG, Von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. *Lancet* 1990;i:1175–8.

33 Severi S, Orsini E, Marraccini P, Michelassi C, L'Abbate A. The basal electrocardiogram and the exercise stress test in assessing prognosis in patients with unstable angina. *Eur Heart J* 1988;9:441–6.

34 Sclarovsky S, Rechavia E, Strasberg B, *et al*. Unstable angina: ST segment depression with positive versus negative T wave deflections—Clinical course, ECG evolution, and angiographic correlation. *Am Heart J* 1988; 116:933–41.

Br Heart J 1992;67:402–5

HLA-DR antigen linkage of anti-β receptor antibodies in idiopathic dilated and ischaemic cardiomyopathy

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Abstract

Objective—Immunological mechanisms have been implicated in the pathogenesis of human dilated cardiomyopathy. The presence of autoantibodies against the β_1 adrenoceptor in a substantial proportion of patients with dilated cardiomyopathy has been described and an association between the HLA-DR4 phenotype and anti-β receptor antibodies has been identified. The objective of the present study was to examine whether the presence of such antibodies in ischaemic cardiomyopathy was limited to specific HLA-DR phenotypes.

Design—The HLA-DR dependence of anti-β receptor antibodies detected by a ligand binding inhibition assay in patients with dilated cardiomyopathy ($n = 68$) was compared with that in patients with ischaemic cardiomyopathy ($n = 73$).

Results—38% of the patients with dilated cardiomyopathy and 22% of those with ischaemic cardiomyopathy had serum anti-β receptor antibodies. In dilated cardiomyopathy, the presence of anti-β receptor antibodies was linked to the HLA-DR4 phenotype (that is, 50% of patients with this phenotype were antibody positive) whereas, in those with ischaemic cardiomyopathy HLA-DR1 was over-represented (that is, 37% of the patients with the HLA-DR1 phenotype were antibody positive compared with 17% of the HLA-DR1 negative patients). In both disease entities, the HLA-DR3 phenotype was virtually absent in the anti-β receptor antibody group.

Conclusions—These results suggest that the presence of anti-β receptor antibodies is under immune genetic control that may depend on the nature of the underlying disease process.

Abnormalities in both cellular and humoral immunity have been repeatedly described in human dilated cardiomyopathy and support the involvement of autoimmune mechanisms in the pathogenesis of this disorder.[1–3] The specific targets of the presumed autoimmune response have not been clearly defined, but are thought to include several cell surface and intracellular constituents. Recently, we,[4] as well as others,[5] have described the presence of antibodies directed against the β_1 adrenergic receptor in a substantial proportion (about 30%) of patients with idiopathic dilated cardiomyopathy. These antibodies inhibit both ligand binding to membrane β receptors[4] and isoproterenol sensitive adenylate cyclase activity.[6] Their presence is linked to the HLA-DR4 phenotype[6 7] suggesting that the increased frequency of this phenotype in dilated cardiomyopathy may reflect the presence of immune genetic factors controlling the propensity to develop autoantibodies.

The frequency of anti-β receptor antibodies in ischaemic heart disease is much lower than that in idiopathic dilated cardiomyopathy.[4] Furthermore, it is not known whether the same immune genetic influences are responsible in both diseases, that is whether the preponderance of HLA-DR4 in antibody positive patients is linked to the propensity to develop autoimmunity or to the pathogenesis of the disease. This issue is examined in the present study by comparing the distribution of HLA-DR antigens in patients with dilated cardiomyopathy and with ischaemic heart disease patients both with and without anti-β receptor antibodies.

Patients and methods

We studied 141 patients (aged 38–82, mean 49 for the dilated cardiomyopathy and 53 for the ischaemic cardiomyopathy group) evaluated at the University of Minnesota. In 68 (64 men and four women) the diagnosis was idiopathic dilated cardiomyopathy and in 73 (67 men and six women) it was ischaemic heart disease. All patients had undergone routine clinical and haemodynamic evaluation, including coronary arteriography and cardiac catheterisation, and were similar in severity of cardiac dysfunction. Phenotyping for HLA-DR was carried out using standard lymphocytotoxicity assays as previously described.[8] Statistical evaluation was as described by Svejgaard *et al.*[9] p Values were corrected for the number of antigens tested and associations were judged significant if $p < 0.05$.

The assay for β receptor autoantibodies is based on their ability to inhibit ligand binding to membrane β adrenoreceptors and has been previously described.[4] Briefly, rat cardiac membranes (0·1 to 0·2 mg protein) were incubated with 100-fold serum dilutions in 50 mM Tris-HCl (pH 7·5), 5 mM McC$_{12}$, 0·1 mM phenylmethyl-sulphonylfluoride,

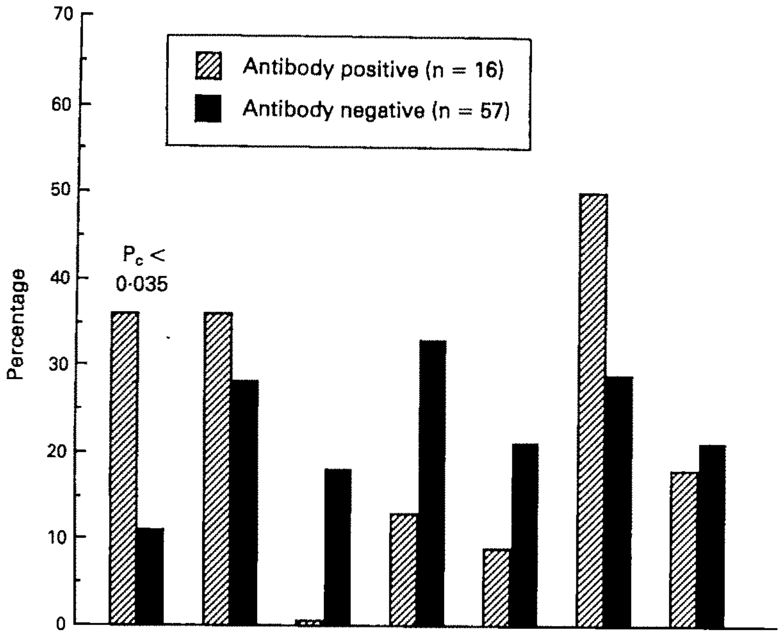

Figure 1 Distribution of HLA-DR antigens in patients with ischaemic cardiomyopathy with or without anti-β receptor antibodies as defined by ligand binding inhibition assay.

5 μg/ml leupeptin, and 7 μg/ml pepstatin at 30°C for 60 min, and then with 6 nM [^{3}H] dihydroalprenolol (New England Nuclear Co, specific activity 105 Ci/mmol) for 15 min. Reactions were terminated by filtration through Whatman GF/C fibres. Non-specific binding was determined in the presence of 1 μM propranolol. Positive results were defined as ⩾20% inhibition of ligand binding in the presence of 100-fold serum dilution.

Results

Anti-β receptor antibodies were present in 38% (26 of 68) of patients with dilated cardiomyopathy compared with 22% (16 of 73) of patients with ischaemic heart disease. Figure 1 shows the distribution of HLA-DR antigens in antibody positive and negative patients with ischaemic cardiomyopathy. There is a significant over-representation of HLA-DR1 phenotype (37% of antibody positive subjects typed as HLA-DR1 compared with 11% of those who were antibody negative ($Pc < 0·035$)) while DR3 is distinctly less frequent. By comparison, anti-β receptor antibody positive patients with dilated cardiomyopathy were more likely ($Pc < 0·02$) to belong to the HLA-DR4 phenotype (fig 2). Although two thirds (6/9) of the HLA-DR1 patients were antibody positive, the numbers were too small to reach statistical significance.

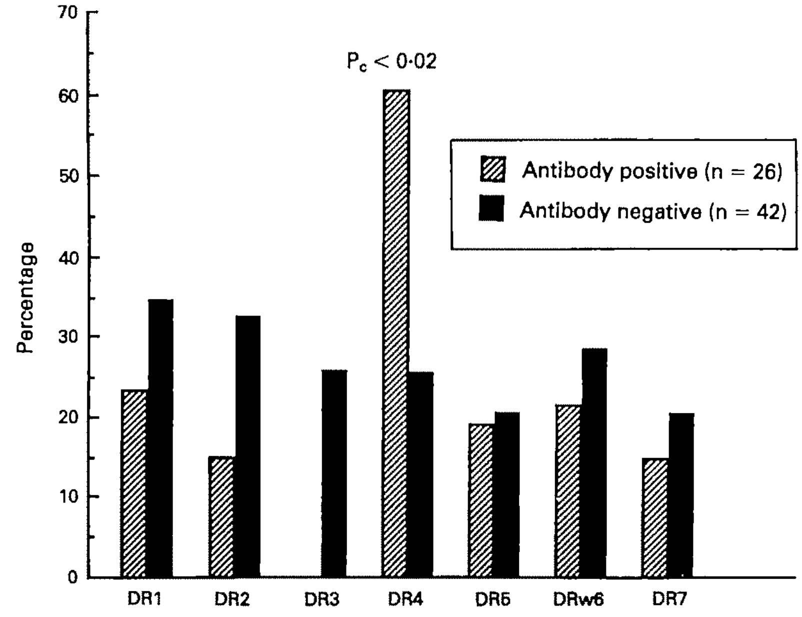

Figure 2 Distribution of HLA-DR antigens in patients with dilated cardiomyopathy with or without anti-β receptor antibodies as defined by ligand binding inhibition assay.

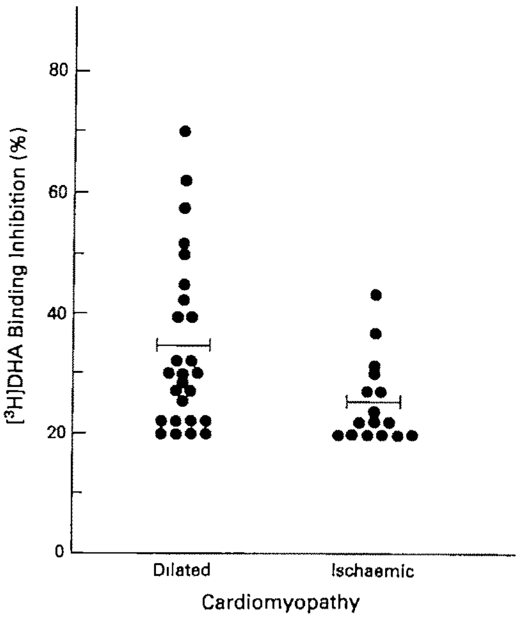

Figure 3 Extent of [^{3}H]dihydroalprenolol (DHA) binding inhibition by 100 fold serum dilutions from patients with dilated or ischaemic cardiomyopathy. The extent of inhibition is related to [^{3}H]DHA binding to control cardiac membranes (incubated in the absence of serum).

In an alternative approach the antibody status of the HLA-DR1 positive and negative patients was considered. In ischaemic cardiomyopathy, 37% (6/16) of the HLA-DR1 positive patients had anti-β receptor antibody compared with 17% (10/57) of the HLA-DR1 negative patients. In dilated cardiomyopathy 50% of the HLA-DR4 patients were antibody positive while only 24% of the HLA-DR4 negative patients were antibody positive. In both disease groups, HLA-DR3 was essentially absent in the antibody positive group. There was a small but significant difference ($p < 0·05$) in the extent of ligand binding inhibition between ischaemic (24·7 (2·0)%) and dilated cardiomyopathy (33·5 (3·0)% groups (fig 3).

Discussion

We have recently shown that a substantial proportion of patients with idiopathic dilated cardiomyopathy have autoantibodies directed against their β adrenoreceptors as judged by their ability to inhibit ligand binding to the receptor and to modify adenylate cyclase activity.[4] This finding was recently confirmed by

Magnusson *et al* using a synthetic β_1 receptor peptide as antigen in enzyme linked immunoassays.[5] It is likely, therefore, that the presence of anti-β receptor antibodies may explain the decline in the density of cardiac β receptors and the reduced inotropic responsiveness to β agonists that characterise dilated cardiomyopathy.[10] It is not known whether the presence of anti-β receptor antibodies can predict the response of cardiac β receptors to agents inducing up regulation (such as β blockers and converting enzyme inhibitors).

The pathogenesis of the antibody response in these patients remains conjectural. Immune disturbances have been described in both experimental and human cardiomyopathy and may be under genetic control. Recently, we[11] as well as others,[12] have reported that the proportion of patients with HLA-DR4 antigens is high in dilated cardiomyopathy. As it is likely that this disease is a heterogeneous entity, the patients with HLA-DR4 antigens may belong to a specific subset in which immunological abnormalities play a predominant role. This proposal is supported by our finding that most of the antibody positive patients belong to the HLA-DR4 or HLA-DR1 phenotype and that, conversely, a substantially higher proportion of HLA-DR4 patients have autoantibodies compared with those without HLA-DR4.[7] These results may be interpreted as evidence that immunogenetic factors linked to the HLA-DR system control the development of anti-β receptor antibodies. Alternatively, the association of such antibodies with HLA-DR4 may be a consequence of the link between this particular phenotype and the susceptibility to dilated cardiomyopathy. If the first alternative were true, the appearance of anti-β receptor antibodies in cardiac diseases of other aetiologies would also be linked to the HLA-DR4 phenotype whereas, if the second possibility were true, the association with HLA-DR4 would hold only for the dilated cardiomyopathy.

To examine this issue we relied on our previous findings that a small proporton of patients with ischaemic heart disease also have anti-β receptor antibodies,[4] and ischaemic cardiomyopathy is associated with a significantly increased frequency of HLA-DRw6 (but not HLA-DR4) antigen.[13] It was possible, therefore, to compare the HLA-DR dependence of anti-β receptor antibodies in these two groups of patients. The results of our study show differences in both the frequency of anti-β receptor antibodies and their HLA-DR dependence between ischaemic and dilated cardiomyopathy. About 38% of the dilated cardiomyopathy patients had antibodies detectable with the ligand binding inhibition assay compared with 22% of these with ischaemic heart disease. In both groups, there was a striking negative correlation between the presence of antibodies and the HLA-DR3 phenotype, raising the possibility that HLA-DR3 may have a protective influence against the development of autoantibodies. It is likely that the antibody response is secondary to an initial myocyte damage (neither ischaemia or cardiomyopathy) and this is more prone to occur in patients without the HLA-DR3 phenotype. The higher frequency of antibodies in dilated cardiomyopathy may reflect differences in the type of autoantigen exposure.

Associations with HLA-DR have typically been described in diseases for which an autoimmune aetiology has been either shown or strongly suggested.[14] For at least some cases of dilated cardiomyopathy, a plausible role for autoimmunity has been suggested, this involves an initial cardiac damage (possibly virus induced) that exposes autoantigens, induction of abnormal expression of class II HLA antigens, and presentation of autoantigens to T lymphocytes.[2] An immunological component to the progression of coronary artery disease has also been suggested, primarily on the basis of the presence of T lymphocytes and macrophages in atherosclerotic lesions.[15 16] A substantial proportion of these cells are immunoactivated as indicated by expression of HLA-DR and interleukin 2 receptor molecules. The extent and frequency of autoimmune responses in atherosclerotic heart disease are currently unknown. It is possible that genetic influences, operating beyond the level of the recognised "risk" factors for development of coronary artery disease, may control immune mechanisms. In our earlier study, the presence of the HLA-DRw6 phenotype in patients with ischaemic heart disease correlated most closely with family history of heart disease and not with the other risk factors, such as lipid abnormalities, diabetes, smoking, or hypertension.[13]

The different HLA-DR dependencies of anti-β receptor antibodies in the two diseases (dilated and ischaemic cardiomyopathy) would appear, at first glance, to argue against a common susceptibility of these patients to develop autoimmune responses. On the other hand, because the HLA-DRw6 phenotype, which is over-represented in ischaemic cardiomyopathy,[13] was not linked to the presence of anti-β receptor antibodies, a link between HLA-DR phenotypes and anti-β receptor antibodies and the pathogenesis of the cardiomyopathy cannot be supported. Also, as there is evidence that HLA-DR4 and HLA-DR1 share common epitopes,[17] it is likely that susceptibility to autoimmunity in dilated cardiomyopathy is linked primarily to these epitopes. If this were the case, development of anti-β receptor antibodies in dilated and ischaemic cardiomyopathy would be under the same immune genetic control. Further studies are needed to clarify this issue.

We thank Drs Maria-Teresa Olivari, Spencer H Kubo, and Gary S Francis for permission to report their patients.

1 Lowry PJ, Gammage MD, Gentle TA, Baynham MID, Thompson RA, Little WA. Suppressor T lymphocyte function in patients with idiopathic congestive cardiomyopathy. *Br Heart J* 1987;57:458–61.
2 Itagaki T, Yamakawa K, Ono S, Yoshinaga T, Umemoto S, Fukuta S, *et al.* Dilated cardiomyopathy associated with natural killer cell deficiency. *Am Heart J* 1988;115:1326–38.
3 Caforio ALP, Bonifacio E, Stewart JT, Neglia D, Parodi O, Bottazzo GF, *et al.* Novel organ-specific circulating cardiac autoantibodies in dilated cardiomyopathy. *J Am Coll Cardiol* 1990;15:1527–34.

4 Limas CJ, Goldenberg IF, Limas C. Autoantibodies against β-adrenoceptors in human idiopathic dilated cardiomyopathy. *Circ Res* 1989;64:97–103.

5 Màgnusson Y, Marullo S, Hoyer S, Waagstein F, Andersson B, Vahine A, *et al.* Mapping of a functional autoimmune epitope on the β_1-adrenergic receptor in patients with idiopathic dilated cardiomyopathy. *J Clin Invest* 1990;86:1658–63.

6 Limas CJ, Goldenberg IF, Limas C. Influence of anti-β-receptor antibodies on cardiac adenylate cyclase in human dilated cardiomyopathy. *Am Heart J* 1990;119:1327–27.

7 Limas CJ, Limas C, Kubo SH, Olivaari MT. Anti-beta-receptor antibodies in human dilated cardiomyopathy and correlation with the HLA-DR antigens. *Am J Cardiol* 1990;5:483–7.

8 Terasaki PI, Clelland JD. Microdroplet assay of human serum cytotoxins. *Nature* 1964;204:998–1000.

9 Svejgaard A, Platz P, Ryder LP, HLA and disease, 1981. *Immunol Rev* 1983;70:193–218.

10 Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Assessment of the β-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and subsensitivity to agonist response. *Circulation* 1986;74:1290–302.

11 Gown AM, Tsukada T, Ross R. Human atherosclerosis, II. Immunocytochemical analysis of the cellular composition of human atherosclerotic lesions. *Am. J Pathol* 1986; 125:191–207.

12 Carlquist JF, Menlove RL, Murray MB, O'Connell JB, Anderson JL. HLA class II (DR and DQ) antigen associations in idiopathic dilated cardiomyopathy. Validation study and meta-analysis of published HLA association studies. *Circulation* 1991;83:515–27.

13 Limas CJ, Limas C. HLA-DRw6 linkage in chronic congestive heart failure secondary to coronary artery disease (ischemic cardiomyopathy). *Am J Cardiol* 1988;62:483–7.

14 Tiwari JL, Terasaki PL. *HLA and disease associations*. New York: Springer Verlag, 1985.

15 Van Der Wal AC, Das PK, Van De Berg DB, Van der Loos CM; Becker AE. Atherosclerotic lesions in humans. In situ immunophenotypic analysis suggesting an immune mediated response. *Lab Invest* 1989;61:166–70.

16 Limas CJ, Limas C. HLA antigens in idiopathic dilated cardiomyopathy. *Br Heart J* 1989;62:379–83.

17 Seyfried CE, Mickelson E, Hansen JA, Nepom GT. A specific nucleotide sequence defines a functional T cell recognition epitope shared by diverse HLA-DR specificities. *Hum Immunol* 1988;21:289–99.

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CASE REPORTS

Atrial myxoma: tumour or trauma?

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Abstract

A mass lesion developed in the right atrium at the site of a trans-septal puncture after percutaneous balloon dilatation of the mitral valve in a man aged 74. The lesion had the pathological appearance of an atrial myxoma and seemed to have developed after trauma to the intra-atrial septum.

This case suggests that at least some atrial myxomas are reactive rather than neoplastic in origin.

Case report

The patient, a 74 year old man, had acute rheumatic fever as a child. He presented with heart failure and atrial fibrillation aged 61. Mitral stenosis was diagnosed and he was treated successfully with digoxin, diuretics, and warfarin.

Signs and symptoms of mitral stenosis progressed over the next 11 years until he was admitted to hospital in April 1988 aged 72 with breathlessness at rest and signs of congestive cardiac failure. Cross sectional echocardiography confirmed severe calcified mitral stenosis with an enlarged left atrium, right ventricle, and right atrium. No other intracardiac abnormalities were detected (fig 1A). His poor general condition and severe chronic obstructive pulmonary disease (forced expiratory volume in the first second 0·7 litres) was thought to preclude surgical valve replacement and he was considered for balloon dilatation of the mitral valve. As part of his assessment for valve dilatation multiple echocardiographic views of both atria and the intra-atrial septum were obtained to exclude the presence of intra-atrial clot. No abnormality was detected within either atrium at this time.

Percutaneous balloon dilatation of the mitral valve was performed on 7 April 1988. The haemodynamic findings were mean transmitral gradient 11 mm Hg, pulmonary artery

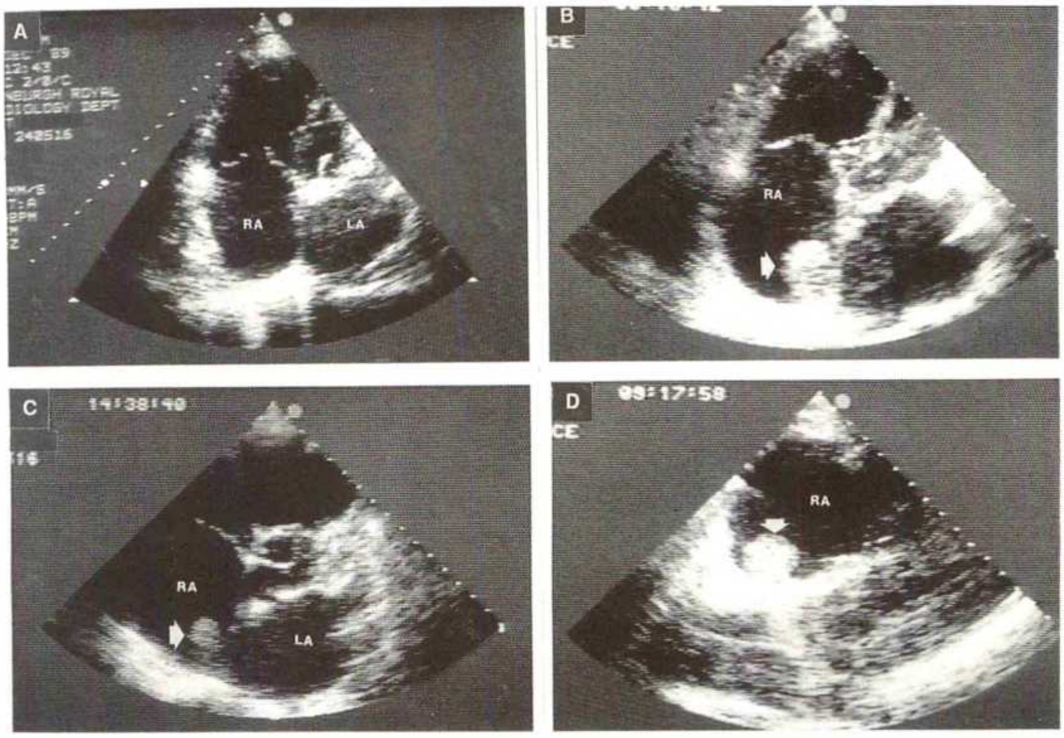

Figure 1 (A) Apical four chamber echocardiogram obtained before balloon dilatation of the mitral valve showing a heavily calcified rheumatic mitral valve, a large left atrium (LA), volume loaded right ventricle and right atrium (RA), but no evidence of a right atrial mass lesion. (B) Preoperative apical four chamber echocardiogram showing a large mass lesion in the right atrium (RA) attached to the intra-atrial septum (white arrow). (C) Preoperative parasternal short axis echocardiogram showing a mass lesion (white arrow) in the right atrium (RA). (D) Preoperative subcostal echocardiogram showing a mass lesion (white arrow) in right atrium (RA).

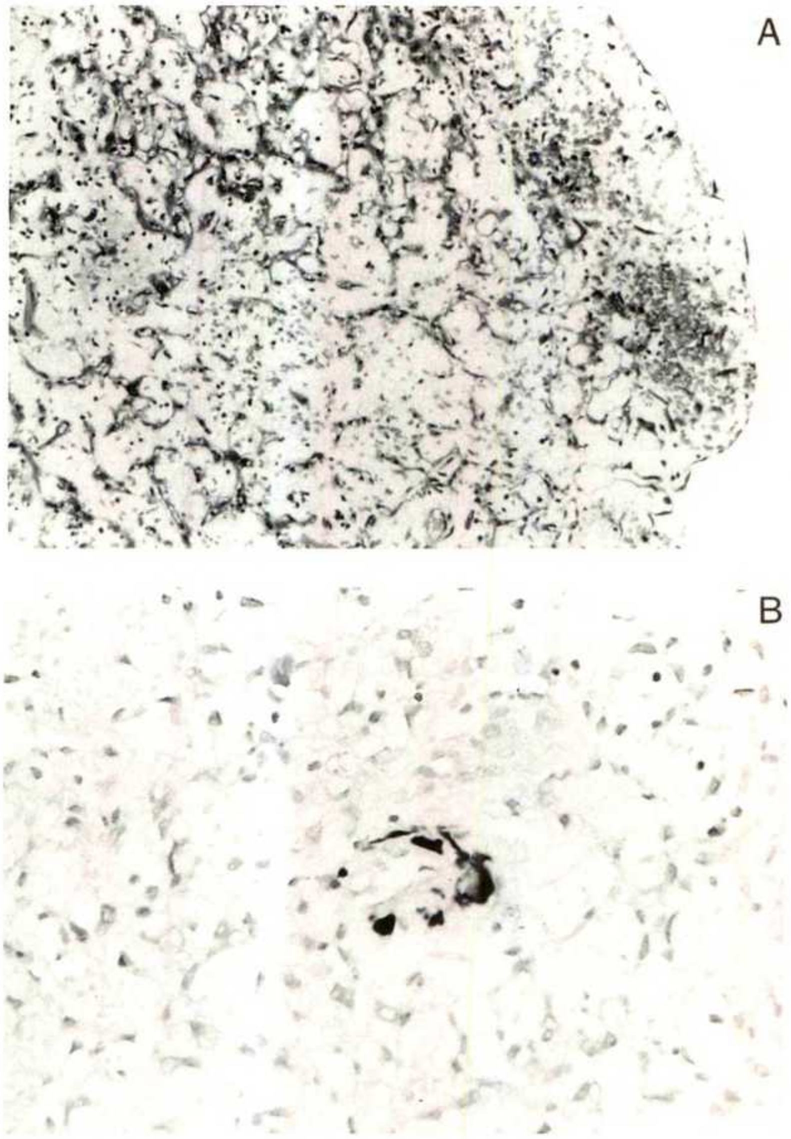

Figure 2 (A) Complex trabecular network of vascular strands within the atrial myxoma (original magnification × 40, haematoxylin and eosin stain). (B) Positive immunohistochemical staining for CAM 5·2, a marker of epithelial differentiation (original magnification, × 100, CAM 5·2).

pressure 66/30 mm Hg, and cardiac index 2·23 l/min/m^2. The coronary arteries were normal and left ventricular function was good. The procedure was initially uneventful, but after three dilatations of the mitral valve acute tamponade developed owing to a perforation of the left ventricle. Emergency thoracotomy was undertaken and a left ventricular tear was repaired successfully. The patient made a satisfactory recovery from this procedure and was subsequently discharged home. At follow up in the outpatient clinic his exercise capacity remained unacceptably limited by his unrelieved severe mitral stenosis.

Because of his persisting severe symptoms the patient was considered for elective mitral valve replacement. As part of his preoperative assessment echocardiography was repeated on 27 April 1989. This study showed a pedunculated lesion in the right atrium attached to the intra-atrial septum at the site of the previous trans-septal puncture. This lesion was large, easily visible, and present in multiple views (fig 1B, C, and D).

At operation on 7 August 1989 his heavily calcified stenotic mitral valve was replaced with a Carpentier-Edwards prosthesis. Within the right atrium was a pedunculated mass measuring 3 cm by 2 cm attached to the intra-atrial septum at an area of obviously abnormal endothelium thought to be the site of the trans-septal catheterisation. The mass and the abnormal endothelium were resected uneventfully.

PATHOLOGY

Histological examination of the resected tissue showed a somewhat lobulated contour to a lesion containing polygonal and stellate cells, forming cords, clusters, and vascular channels within a loose myxoid matrix. In some areas there were dense trabecular networks of intercommunicating strands (fig 2A). There was focal haematopoiesis and the stroma was alcianophilic. Immunohistochemistry showed positive staining for Factor VIIIrAg (Dako, Buckinghamshire) which was most prominent in the lining of the vascular channels. There was widespread positivity for vimentin (Dako) and intense staining of single cells for PGP 9·5 (Ultraclone, Cambridge), and NSE (Dako). There was focal positivity for CAM 5·2 (Becton Dickinson, Oxford), a marker of epithelial differentiation (fig 2B). The appearances were those of an atrial myxoma.

Discussion

There is still controversy about the pathogenesis of atrial myxoma. Occasional cases with chest wall invasion,[1] distant metastases,[2] or chromosomal abnormalities,[3] suggest that some at least are neoplastic. Histologically, however, atrial myxoma has features in common with organising thrombus and some workers maintain that it is essentially a reactive proliferative phenomenon.[4] Indeed distinguishing myxoma from thrombus can occasionally pose problems for the pathologist. Myxomas have also been reported to show osseous, chondroid, and even glandular[5] differentiation.

The myxoma in our patient, as well as having a population of bizarre mesenchymal cells within a loose myxoid matrix, also contained foci of haematopoiesis and had immunohistochemical evidence of epithelial differentiation. Such features would be most unlikely in thrombus and warrant a diagnosis of myxoma.

This right atrial myxoma seems to have developed after iatrogenic trauma to the atrial septum. The lesion seems to have developed rapidly over a 12 month period between the pre-dilatation and preoperative echocardiograms. It is unlikely that the lesion was present but not seen on the echocardiogram before the attempted balloon dilatation. Neither of the two separate echocardiographic examinations performed before the procedure with multiple views of both atria and the intra-atrial septum showed a lesion. All the echocardiographic recordings in this patient were performed by the same experienced operator. Furthermore, the mass lesion subsequently detected was large and easily visualised in three separate standard echocardiographic views.

This association has not been reported before, despite the fact that trans-septal puncture is a relatively common procedure worldwide; this may reflect the fact that such an association is uncommon. The degree of trauma to the intra-atrial septum caused by balloon dilatation of the mitral valve is greater than that occurring in diagnostic septal punctures and this may provide a greater stimulus for the development of a reactive lesion. Close echocardiographic surveillance of patients after balloon dilatation of valves may shed more light on the incidence of this complication.

This lesion, which had clear cut pathological features of an atrial myxoma, seems to have developed in a 12 month period between two consecutive echocardiograms. The close temporal relation with atrial septal trauma in this patient supports the concept that local tissue injury initiates cell proliferation in the endocardium.

We believe that it is important to alert interventional cardiologists to the occurrence of this phenomenon and we hope that by doing so more information will be gathered about the incidence of myxoma after iatrogenic trauma to the heart. In addition our case serves to reopen the debate about the pathogenesis of intracardiac myxomas.

We thank Mr C Campanella for his help in preparing this paper.

1 Read RC, White HJ, Murphy ML, Williams D, Sun CN, Flanagan WH. The malignant potentiality of left atrial myxoma. *J Thorac Cardiovasc Surg* 1974;68:857–68.
2 Seo IS, Warner TFCS, Colyer RA, Winkler RF. Metastasizing atrial myxoma. *Am J Surg Pathol* 1980;4:391–9.
3 Dewald GW, Dahl RJ, Spirbeck JL, Carney JA, Gordon H. Chromosomally abnormal clones and non-random telomeric translocations in cardiac myxomas. *Mayo Clin Proc* 1987;62:558–67.
4 Salyer WR, Page DL, Hutchins GM. The development of cardiac myxomas and papillary endocardial lesions from mural thrombus. *Am Heart J* 1975;89:4–17.
5 Goldman BI, Frydman C, Harpaz N, Ryan SF, Loiterman D. Glandular cardiac myxomas. Histologic immunohistochemical and ultrastructural evidence of epithelial differentiation. *Cancer* 1987;59:1767–75.

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Endocarditis with aneurysm involving an aortic homograft used to correct a truncus arteriosus: medical-surgical salvage

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Abstract

An aneurysm of an aortic homograft conduit, used to correct a type I truncus arteriosus anomaly in a four month old infant, developed when the patient was 15. Blood cultures grew *Staphylocuccus aureus*. The aneurysm was detected by magnetic resonance imaging and digital subtraction angiocardiography. An emergency open heart operation, guided by these investigations, was performed to remove the original homograft and replace it with another valved aortic homograft. Postoperative antibiotic treatment had to be stopped when profound neutropenia developed. This responded to treatment with recombinant human granulocyte colony stimulating factor.

Three years later she was symptom free and did not require medication. Chest *x* rays and echocardiograms showed a normally functioning heart and conduit valve.

We report the successful outcome of two life-threatening events 15 years after placement of an aortic homograft conduit to repair a truncus arteriosus.

Case report

HISTORY

An aortic homograft and closure of the ventricular septal defect were used to repair a type I truncus arteriosus in a four month old baby who was born prematurely and weighed 1390 g at birth and 3 kg at surgery.[1] She did well under regular cardiological follow up, though the conduit became calcified and systolic and diastolic murmurs of conduit valve stenosis and regurgitation developed. Cardiac catheterisation when she was three years old and seven years old showed gradients across the homograft of 28 and 25 mm Hg respectively between the right ventricle and pulmonary artery. Doppler echocardiography at 10 and 13 years showed a systolic pressure drop of 44 mm Hg along the conduit. Magnetic resonance imaging at 12 years displayed flow through the conduit.

PRESENT ILLNESS

At the age of 15 she had fever for one week, which did not respond to oral erythromycin. Examination showed splenomegaly and the systolic and early diastolic murmurs noted earlier. The cardiac contour and size as well as pulmonary vascularity and parenchyma were normal on the radiograph. Continuous wave Doppler echocardiography showed a pressure drop of 100 mm Hg at the proximal end of the conduit. Blood cultures grew *Staphylococcus aureus* that was resistant to erythromycin but sensitive to nafcillin, gentamicin, and vancomycin.

COURSE

Despite treatment with intravenous nafcillin and gentamicin, temperature spikes persisted each afternoon. Over the next four days she developed bilateral pleural effusions, pericardial effusion, and signs of right-sided cardiac failure. Digoxin and diuretics were added to the regimen. Three days later a chest *x* ray showed nodular densities in both lung fields and a rounded prominence in the region of the outflow tract of the right ventricle that rapidly increased in size. A computed tomographic scan of the chest, with contrast enhancement, identified pleural and pericardial effusions as well as infiltrates in the lower lobes. Digital subtraction angiocardiography (DSA) (fig 1) and magnetic resonance imaging (MRI) (fig 2)

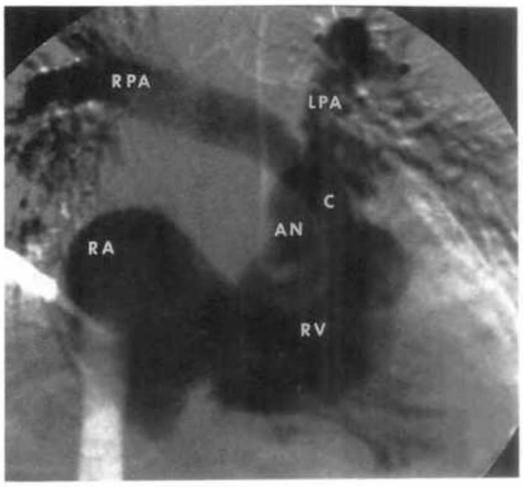

Figure 1 Digital subtraction angiocardiogram showing the aneurysm (AN) superimposed on the conduit (C). The aneurysm continued to the left and right pulmonary arteries (LPA, RPA) and the right atrium (RA) and ventricle (RV) were dilated.

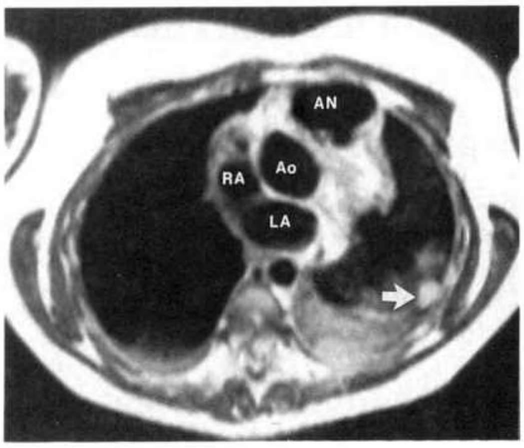

Figure 2 Magnetic resonance imaging (axial view) showing maximal dilatation of the aneurysm (AN) and its relation to the overlying sternum and to the aortic root (Ao) and the right and left atria (RA and LA). An arrow points to the infarct. Pleural effusions were present.

confirmed the suspicion of aneurysm where the conduit connected with the right ventricle and of haemorrhagic infarcts in both lung fields with bilateral pleural effusions.

SURGERY

Open heart surgery was undertaken as an emergency to remove the aneurysm and the original homograft and replace it with another valved aortic homograft. Because MRI and DSA had shown that the aneurysm was contiguous anteriorly with the sternum (fig 2) a right thoracotomy was used for cannulation of the venae cavae and aorta. When the median sternotomy incision was reopened and the sternum divided, the aneurysm was indeed entered, but cardiopulmonary bypass was immediately started and bleeding controlled. The thin walled aneurysm originated from the right ventricle proximal to the graft, which was obstructed by granulation tissue proximally but was patent and densely calcified. The conduit was removed and the pulmonary artery branches were enlarged to accommodate the new, size 21 cryopreserved aortic homograft. Systolic pressure measured in the right ventricle when the patient's condition was stable off bypass was less than half systemic pressure. Microscopy of the removed graft showed calcified, focally necrotic connective tissue containing many Gram positive cocci. The aneurysm contained dense connective tissue and granulation tissue with acute and chronic inflammation. Cultures yielded no growth.

Relation of white blood counts to operation and treatment with granulocyte stimulating factor (GSF)

Day postop	*White blood cells/μl*	*Absolute neutrophil count/μl*	*Day of GSF*
0	14 600	12 100	
3	11 100	10 700	
6	4500	4100	
7	3100	2480	
8	1200	620	
9	1000	160	
10	600	0	0
12	400	0	1
13	600	0	2
14	1000	0	3
15	2600	30	4
16	4000	1200	5
17	4700	3290	6
18	10 900	8070	7
19	7300	5620	8

POSTOPERATIVE COURSE

Treatment with nafcillin and gentamicin was continued. On the third postoperative day when a rash appeared, intravenous amikacin replaced gentamicin. Neutropenia began to develop on the sixth day (table); so nafcillin was stopped and vancomycin started. Three days later, oral ciprofloxacin was added. Her temperature rose intermittently to 39·6°C. Neutropenia became profound: total white blood cells 400–600/μl with absolute neutrophil counts of 0 (table). A bone marrow biopsy specimen was markedly hypocellular, with fully maturing erythroid elements and megakaryocytes but virtual absence of myeloid elements. The peripheral blood did not contain neutrophil antibodies.

We obtained permission from the Food and Drug Administration, from the manufacturers (AMGEN), and from the Institutional Committee on Human Rights in Research for the compassionate use of recombinant human granulocyte colony stimulating factor (rhG–CFS).[2] Recombinant rhG–GSF in a daily dose of 3 μg/kg per day was chosen because of previous experience in children with congenital or chemotherapy-induced neutropenic disorders.[2 3] This agent was administered subcutaneously for 14 successive days. The white blood cell count began to increase (table) to a normal number of white blood cells and neutrophils by the seventh day of treatment with rhG-CSF. After two weeks the count reached 15 800/μl. As the count rose she became afebrile and continued so. After the fifth day without fever she was discharged; she was treated oral ciprofloxacin for two more weeks.

In the next three years she remained symptom free and did not require medication. Chest *x* ray showed that the size and contour of the heart were normal, and echocardiography showed normal function of the myocardium and conduit valve.

Discussion

This patient had endocarditis with a rapidly expanding aneurysm, considerable obstruction to right ventricular outflow, and emergency cardiac surgery. She also had another life-threatening complication—a severe reaction to one or more of the intravenous antibiotics needed to control the infection.

When the aneurysm appeared and expanded during the course of antibiotic treatment, two non-invasive diagnostic tests (DSA and MRI) showed the proximity of the aneurysm to the overlying sternum and this information helped us to plan the life-saving operation. A review of 143 episodes of endocarditis in children between 1950 and 1988 noted that 23 patients needed cardiac surgery, seven of these for resections of infected areas, chiefly related to the ductus or coarctation of the aorta.[4]

When profound neutropenia appeared we sought permission to use a regulatory glycoprotein that stimulates neutrophil granulocyte production from committed haematopoietic progenitor cells both in vitro and in vivo. In addition it modulates multiple differential functions of mature neutrophils.[5] Thus this agent enabled her neutrophils to recover and to function.

Medical and surgical management enabled a patient as an infant to survive not only considerable prematurity but also open heart surgery by a new procedure (to construct a pulmonary artery conduit) not previously carried out in such a small baby.[1] In adolescence staphylococcal endocarditis with an expanding aneurysm associated with the homograft and with the profound neutropenia related to the antibiotics responded to medical and surgical treatment.

We thank Dr Peter Kosovsky for magnetic resonance imaging, Dr Eric F Grabowski and Dr Janice O Gabrilove for use of the granulocyte-stimulating factor, Dr John E O'Loughlin and Dr Michael S Snyder for interpreting the echocardiograms, and Mr Richard Fischer for MRI photography.

1 Ebert PA, Robinson SJ, Stanger P, Engle MA. Pulmonary artery conduits in infants younger than six months of age. *J Thorac Cardiovasc Surg* 1976;72:351–6.
2 Gabrilove JL, Jakubowski A, Scher H, Sternberg C, Wong G, Grous J, *et al*. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988;**318**:1414–22.
3 Bonilla MA, Gillio AP, Rugiero M, Kerman NA, Brochstein JA, Abboud M, *et al*. Effects of recombinant human granulocyte colony stimulating factor on neutropenia in patients with congenital agranulocytosis. *N Engl J Med* 1989;**320**:1574–80.
4 Wells WJ. Surgical problems of endocarditis in children. *J Cardiac Surg* 1989;4:313–6.
5 Alvalos C, Hedzat C, Baldwin GC, Golde DW, Gasson JC, DiPersio JF (introduction by Balcerzak SP). Biological activities of human G-CSF and characterization of the human G-CSF receptor [abstract]. 29th Meeting of American Society of Hematology, 5–8 December 1987, Washington DC, page 1.

Br Heart J 1992;67:412–8

BRITISH CARDIAC SOCIETY

Working party report on cardiac rehabilitation

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1 Introduction

1.1 Cardiac rehabilitation can be defined as the process by which patients are restored to and are maintained in their optimal physiological, vocational, and social status. It is a multidisciplinary approach to improve short-term recovery and to promote long-term changes in lifestyle which correct adverse risk factors.

1.2 Ischaemic heart disease remains the commonest cause of cardiac death in western societies and the highest rates in the world are found in parts of the British Isles. In most district general hospitals myocardial infarction and other coronary syndromes are the largest single diagnostic category for patients admitted to general medical beds. For a population of 200 000 this usually means that between 200 and 600 patients per year would be suitable for cardiac rehabilitation depending on the local prevalence of disease. In addition increasing numbers of patients are being treated by coronary artery bypass grafting or angioplasty. Two thirds of these people could be expected to resume their normal daily duties either at work or at home.

1.3 The first cardiac rehabilitation service was set up in the United Kingdom over 20 years ago, but despite the large numbers of patients who might benefit, only a few have facilities available to them now; this is largely because of a divergence of opinion among cardiologists and physicians about the physical and psychological benefits of rehabilitation.

2 Development worldwide

2.1 The finding in the 1950s that coronary patients have responses to exercise that are similar to normal, but modified by deconditioning, led to the use of physical training to aid postinfarction recovery.[1] Israel was the cradle of the large scale rehabilitation effort.[2-4] As early as 1955 Gottheiner[4] stated his approach to training coronary patients and by 1968 had experience of over 1000 patients who had training for at least five years. At the same time Hellerstein and Ford (1957)[5] in Cleveland, Ohio, produced guidelines for cardiac rehabilitation at exercise centres: many of these have not been improved upon since.

2.2 During the 1960s and 1970s coronary rehabilitation spread through North America[6 7] and Europe[8 9] and has now become an established treatment for postinfarction patients in many countries. The trend has moved away from long-term supervised exercise to short courses of physical training after the acute illness with encouragement to patients to continue exercising unsupervised thereafter.

2.3 There is still much disparity between centres in the structure of these programmes; this was partly responsible for the ending of the huge World Health Organisation multicentre controlled trial of postinfarction rehabilitation[10] before any firm conclusions could be reached.

2.4 Even now cardiac rehabilitation means very different things in different countries. In the United States and parts of Europe rehabilitation programmes have a large capital investment which is little less than for a full physiological laboratory and are able to undertake sophisticated objective measures of a patient's progress. In Germany and Italy there are well established inpatient programmes lasting several weeks. In the United Kingdom, by contrast, most programmes are outpatient based, concentrate on patients in the first few months after myocardial infarct or cardiac surgery, and do not attempt to undertake long-term training.

3 Role of exercise

3.1 For many years there has been interest in the relation between coronary heart disease and physical activity. Epidemiological research began almost 40 years ago,[11] but it was not until 1984 that evidence became available that suggested that athleticism reduces the incidence of coronary heart disease.[12] A recent prospective study showed that a low level of physical fitness is an important risk factor in both men and women and that high levels seem to delay all-cause mortality and specifically to reduce mortality caused by cardiovascular disease and cancer.[13]

3.2 In patients with established cardiac disease the evidence for improved survival with rehabilitation is increasing. An overview of 22 randomised trials of exercise based rehabilitation after myocardial infarction in 4554 patients showed a 20% reduction in overall mortality. This was reflected in a decreased risk of cardiovascular mortality and fatal reinfarction for at least three years and a reduction in sudden death for at least a year after myocardial infarction (fig 1).[14] A similar meta-analysis of 10 trials concluded that comprehensive cardiac rehabilitation had a beneficial effect on mortality, but not on non-fatal recurrent myocar-

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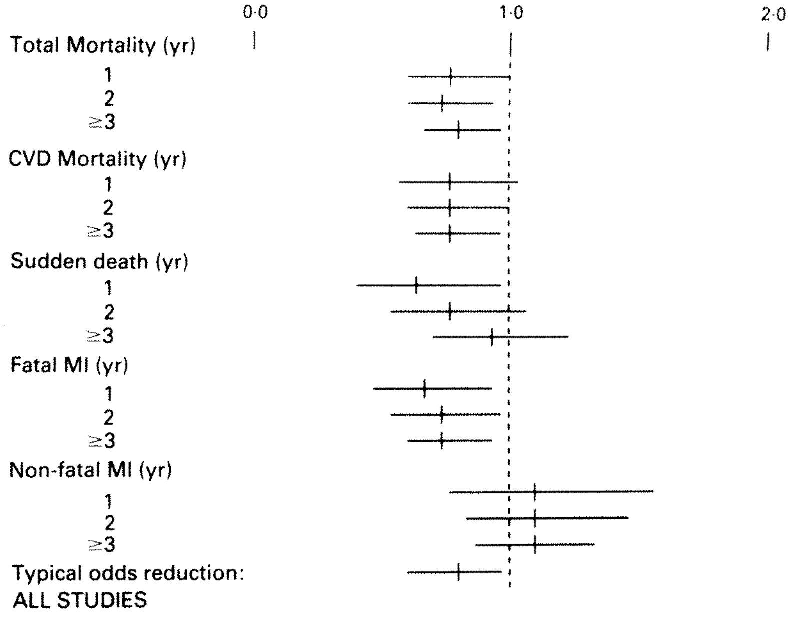

Figure 1 Effect of cardiac rehabilitation on mortality and re-infarction after myocardial infarction. Data taken from the meta-analysis of 22 trials by O'Connor et al[14] *showing the point estimates of the odds reduction (vertical lines) with 95% confidence intervals (horizontal lines).*

dial infarction.[15] These reductions in mortality compare favourably with many other currently accepted treatments in ischaemic heart disease (for example, prophylactic β blockade).

3.3 Dynamic training in a healthy person causes morphological changes in the heart and physiological hypertrophy may occur, with dilatation of all chambers leading to an adaptive net increase in heart size. As a consequence of these changes there is an increase in stroke volume at rest and during exercise. A trained individual will show a higher arteriovenous oxygen difference at maximal values. The catecholamine concentrations of trained individuals are lower for comparable workloads and because of a decrease in sympathetic tone, the heart rate is slower. Consequently the same cardiac work can be performed more economically because heart rate and contractility are important determinants of myocardial oxygen consumption. Slowing of the heart rate also increases the duration of diastole thus increasing myocardial perfusion time, which may have additional protective benefit.

3.4 Many studies have shown an improvement in exercise tolerance with physical training in patients with cardiovascular disease. Yet left ventricular function is often unchanged, lending support to the hypothesis that such improvement is due to peripheral adjustments.[16] Groups of patients undergoing sustained training for longer than one year have shown increases in stroke volume,[17] ejection fraction,[18 19] myocardial contractility, left ventricular end diastolic dimensions; posterior left ventricular wall thickness, and left ventricular mass.[20 21] Given the considerable individual expressions of ischaemic heart disease these factors probably inter-react to a variable degree and further study is required.

3.5 Until recently dynamic training has been the primary method applied to patients with cardiovascular disease. However, recent work has suggested that static (resistance) training can be carried out with safety in coronary artery disease and that beneficial effects can be obtained.[22]

3.6 Early mobilisation after myocardial infarction and coronary artery bypass graft surgery is known to be beneficial,[23 24] although there continues to be debate concerning how soon after a cardiac event exercise training should begin. While some programmes start relatively vigorous exercise training within two to three weeks, most programmes introduce patients within four to six weeks of myocardial damage or cardiac surgery.

3.8 Patients of all ages should be considered for exercise training provided there is no neurological or locomotor deficiency that may hinder performance or predispose to injury. Recent work has shown a definite benefit of exercise training in patients with class II and III heart failure[25] and after transplantation.[26] To date there has been little interest in other groups that could show a similar response.

4 Psychological aspects of rehabilitation

4.1 The medical and psychological outcomes for patients who have had myocardial infarction or bypass graft surgery may be independent of one another. Psychosocial problems have been shown to be common in patients with an otherwise good recovery.[27] Anxiety and depression have been reported in a considerable minority for at least one year after myocardial infarction and are associated with poor occupational and social adjustments.[28] Similar psychological disturbances are common during the early phases of recovery after cardiac surgery and have been shown to inhibit long-term outcome. Disturbed behaviour can be recognised during the stay in hospital, but it is often easiest to identify at risk patients a few weeks later when they have returned home. Those who report distress and poor general progress at this stage are more likely to have continuing problems.

4.2 Some patients minimise the seriousness of their illness by denial; this may improve short-term recovery during the acute phase but these patients may be more vulnerable during transfer or hospital discharge. It has been shown that patients' decisions and behaviour are mainly guided by their personal interpretation of illness,[29] and these assessments may not accord with the physician's view of the patient's state of health. Such discordance can lead to psychological disturbance and prolong the recovery phase. Persistent emotional problems are associated with poor compliance with medical advice and treatment and lead to unnecessary disability. Close relatives often suffer considerable distress and can substantially influence convalescence.

4.3 Many patients are reluctant to bother their doctors with worries about their illness and must be given the opportunity to discuss their concern about the implications of heart disease for the future. Misunderstandings can easily arise because standard booklets and explanations do not meet the patient's own individual fears and needs. Rehabilitation programmes should provide good varied written information supplemented by individual discussion and counselling where needed. Spouses should be active in this process.

4.4 Systematic monitoring of mental state and of progress in physical activity, work, leisure, and sexual expression helps to identify emotional problems early in the rehabilitation course. Determinants include previous psychological problems or poor social adjustment, major cardiac complications, overprotective family, and those patients whose livelihoods depend on physical activity. Recognition of such problems may be more easily discovered from relatives than from the patients themselves. A proportion of such patients need access to more specialist help for stress management, depression, and behavioural treatment.

4.5 Some psychosocial benefits may be obtained by means of physical conditioning,[30] and education; both individual and group counselling together with the provision of stress management strategies and relaxation training are an integral part of many programmes. However, definite evidence of the effectiveness of these approaches is lacking. This lack of information partly reflects the dearth of good measures of outcome and the difficulty in setting up controlled trials in this area. The development of newer and more suitable techniques for the evaluation of the psychological effects of cardiac rehabilitation is necessary and will prove instructive.

5 Vocational aspects

5.1 Return to work is usually an explicit aim of cardiac rehabilitation. Whereas most patients do return to work, reports from most countries indicate that a considerable number of patients fail to return to work after myocardial infarction and bypass graft surgery. Those factors which favourably dispose to return to work are a satisfactory preinfarction work status, high educational level, social ranking, good exercise tolerance, absence of symptoms and the patient's own assessment of physical status.

5.2 Undoubtedly, many aspects of the work environment are beneficial: work gives a sense of purpose and establishes a sense of identity, it provides relationships outside the family, and is a source of obligatory activity and discipline with an opportunity to develop creative skills. These ideal concepts of the workplace, however, are not the experience of all workers and many encounter poor job satisfaction, interpersonal tensions, and communication difficulties; they cannot cope with technological advances and are disturbed by the potential of redundancy. Shift work is a particular problem for patients with cardiac disease.

5.3 Recently published guidelines[31] aimed at increasing the number of patients returing to work emphasise that vocational services need to be involved early in the rehabilitation process because prolonged inactivity can lead to permanent invalidism. To this end, job characteristics should be evaluated—taking into account energy expenditure, psychological stress, risks involved, shift work, the use of heavy or vibratory equipment, and exposure to toxic substances. Good communications between the medical staff and those providing vocational counselling about medical status, exercise tolerance, and psychological outcome are essential because doctors have a major role in deciding whether or not a patient returns to work, and generally base this decision exclusively on physical criteria.

5.4 Most studies have shown that unemployment is greatest in those in the lower socioeconomic sector carrying out physically demanding jobs, and for such patients work assessment units have been shown to be of value in establishing work potential and where possible, directing patients to more suitable employment. Direct contact between vocational counsellors and employers has also been shown to improve the capability to return to work.

5.5 The primary goal of such services must be to return patients to work that is compatible with their functional capability and adjustment may be helped by changing to employment or activity that is more appropriate to their current physical and psychological state. The option of giving up work is often overlooked. The impact of this aspect of vocational counselling on quality of life and longevity deserves evaluation because resumption of work is largely determined by factors such as age, severity of disease, educational level, and adequacy of pension and retirement benefits, which cardiac rehabilitation cannot influence.

6 Setting up a coronary rehabilitation programme

6.1 There is no ideal rehabilitation programme that will encompass the needs of every patient, and most courses evolve to suit the needs of most patients with the resources then available. The programme should offer a range of components with specific advice concerning mobilisation, work, and changes in lifestyle directed at improving prognosis (fig 2). Cardiac rehabilitation should begin as soon as possible within the hospital environment, and the clinician should identify whether the patient falls into a low or high risk group for rehabilitation, preferably with the help of a pre-discharge exercise test. Relevant family members should be involved at these early stages.

6.2 An exercise programme forms the basis around which the various other measures embodied in the rehabilitation concept can be established. Flexibility in terms of early or late entry to the programme is essential, but most patients are ready to join a supervised exercise training programme 4–8 weeks after cardiac surgery or myocardial infarction. Before formal training a symptom limited submaximal (85% maximum) exercise test is recommended. Training methods to sustain heart rates of 70–85% of that achieved at the initial exercise test are provided up to three times a week for at least 30 minutes for 6–12 weeks. Exercise for

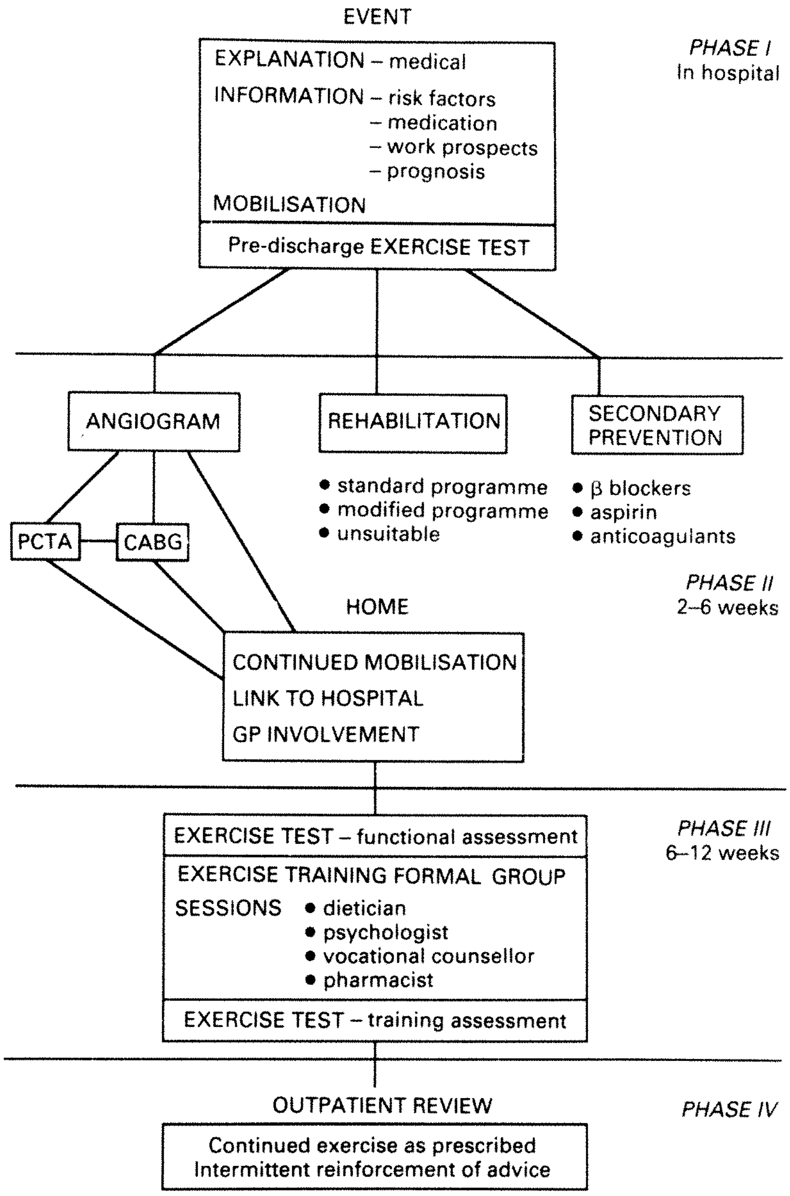

Figure 2 Scheme for patient management incorporating rehabilitation after myocardial infarction or cardiac surgery.

coronary patients should be mainly aerobic and include the use of treadmill, bicycle ergometer, steps, rowing machine, handcrank, jogging, and mini-trampoline. Some strength training can be also applied by the use of light weights. Warmup and cooldown routines are essential. On the days when formal exercise training is not taking place, walking or cycling for not less than 30 minutes is also recommended.

6.3 Training can take place in a hospital gymnasium, physiotherapy department, or a specific area within the department of cardiology, if such is available. Staff should be fully trained in cardiopulmonary resuscitation and relevant medications, and a defibrillator must be to hand. In such an environment continuous electrocardiographic monitoring will be necessary if certain high risk groups participate (table).[32] Community sports centres are also satisfactory areas for the provision of exercise training. A low rate of cardiac complications has been reported for such programmes.[33 34] Low risk patients can perform most of these exercises at home.[35]

6.4 A long-term programme for regular exercise should be available for all patients on completion of the formal exercise training period and a system of regular re-evaluation is recommended because with time many patients return to their previous unsatisfactory lifestyles. With the constraints on hospital resources these more long-term facilities may be more readily available from self help groups in the community. Those running hospital based programmes should, if possible, liaise with those running programmes in the community and establish a standard continuation protocol.

6.5 A nurse or physiotherapist is the most likely person to co-ordinate the rehabilitation programme. Such an individual should be familiar with all the disciplines involved in cardiac rehabilitation and be fully trained in cardiopulmonary resuscitation. The services of a dietitian, psychologist, pharmacist, vocational counsellor, and social worker should be included where appropriate. A continuous medical presence at exercise sessions or educational periods is not essential but regular attendance shows continuing interest in patient welfare, and affords a valuable opportunity to observe progress, alter treatment, and to answer questions.

6.6 Group sessions should be established in association with the formal exercise programme and should include spouses. These sessions should impart information on the nature of coronary artery disease and provide advice on a healthy lifestyle, with specific attention to smoking cessation and risk factor management in general. Work related problems must be addressed individually. Stress management and relaxation therapy should be available and spouse interviews should take place. Simple clearly written literature should be made available and discussed.

6.7 It may not be necessary for all patients to be exposed to every aspect of the rehabilitation programme. Selective use of areas where specific advice and intervention are perceived necessary can be valuable, and extended use of these facilities should be made available to the minority of patients requiring them. This may be important for women and certain ethnic groups who may find the standard exercise programme unappealing or even intimidating.

6.8 The capital costs of setting up a rehabilitation programme are relatively small, given that most Health Districts have access to adequate gymnasium facilities either within the hospital or outside. Little extra equipment is required unless it is decided to monitor the high risk individual by telemetry. Staff costs will depend on the complexity of the programme, the number of patients, and the duration of treatment. Experience from within

High risk patients who may require more intensive monitoring during cardiac rehabilitation

Survivors of sudden cardiac death, especially if unrelated to infarction
Low left ventricular ejection fraction (< 35%)
Complex ventricular arrhythmias, especially if exercise related
Exercise induced hypotension
Continuing effort angina
Positive exercise test (> 2 mm ST depression)

the working party suggested that approximate running costs per patient session were £15 for a fully monitored unit in a cardiac centre, £5 for a district hospital, and £4 for a community based programme.

6.9 At present there is no nationally co-ordinated scheme for training in cardiac rehabilitation, and those interested in starting a course usually visit another centre informally or attend one of the courses held periodically at one of the established centres. Counselling is an important aspect of rehabilitation which at present is often carried out in an amateur fashion through lack of more formal training.

7 Current facilities in the British Isles

7.1 Cardiac rehabilitation programmes were identified by a preliminary enquiry sent by the Coronary Prevention Group to 268 cardiac care/intensive care units in the United Kingdom and Republic of Ireland listed in the *Directory of Emergency and Special Care Units*. This was followed by a more detailed questionnaire sent in mid-1989 to the individual (usually the consultant, nurse, or physiotherapist) identified as being in charge of the programme. A total of 91 established outpatient programmes were identified: 88 in hospitals (87 in the United Kingdom and one in the Republic of Ireland), and three in the community. These figures show that considerably less than half the Health Districts in the British Isles have an established rehabilitation programme.

7.2 Although some courses had been established for almost 20 years, an increasing number of programmes had been established in the past five years, 32 of them in the previous two years (fig 3). The size of these programmes varied considerably; the numbers of patients completing outpatient cardiac rehabilitation in the year January to December 1988 were as follows: less than 50 patients/year, 14 centres; 50–100 patients/year, 27 centres; 100–200 patients/year, 17 centres; 200–500 patients/year, 14 centres. Most centres treated patients after both myocardial infarction and coronary artery bypass surgery. Twenty two centres also catered for patients after valve surgery or transplant; 14 of these were centres for cardiac surgery.

7.3 Programmes at 50 centres had been started at the request of a consultant; the remainder were requested by a nurse or physiotherapist. There was continuing involvement of the consultant in 61 hospitals; a cardiologist was involved in only 27 of the 61 programmes.

7.4 Physiotherapists were involved in 75 programmes, dietitians in 65, nurses in 37, occupational therapists in 19, psychologists in 20, social workers in eight, general practitioners in six and employment advisers in one programme. Sessional commitments for all disciplines were usually 1–2 hours, with physiotherapists involved each week and others attending once or twice a month.

7.5 Most programmes (75) defined some exclusion criteria. There was an age limit in 47. No centres excluded women, but several recorded problems for women who attended. These included family commitments, difficulties with transport, and embarrassment in sessions with a predominance of men. The commonest cardiac conditions to be excluded were arrhythmias, cardiac failure, and angina.

7.6 Most courses organised rehabilitation in groups. Patients generally started within four weeks of myocardial infarction, but a little later after cardiac surgery, and courses lasted 4–12 weeks. Sessions usually lasted 1–2 hours and were held 1–6 times per week. Five centres included specific relaxation sessions. Sixty four programmes included counselling in the sessions, usually with the spouse. In addition 39 centres had a local self help group; in 24 this was based in the community and in 15 in the hospital.

7.7 Formal exercise testing was carried out as a routine in only 28 centres before and only 17 after cardiac rehabilitation, though most (79) carried out exercise testing in selected patients.

7.8 Staff trained in cardiopulmonary resuscitation were present during sessions at all but two centres, and resuscitation equipment available in all but four. There was medical supervision during sessions in 58 centres; in 29 this was a doctor and in 35 a nurse. All but six centres undertook some form of patient monitoring; in most this was simply pulse or blood pressure, but 10 had full electrocardiographic monitoring. Only 44 centres reported that they had experienced any incidents during an exercise session. Serious reactions were reported from only seven centres in the past year; one myocardial infarction, five cardiac arrests, and two deaths (one centre had two incidents).

7.9 The drop-out rate was estimated to be less than 10% in most centres (60 out of 76 responding). Motivation, transport, medical problems, and interference with returning to work were all regarded as important reasons for non-attendance.

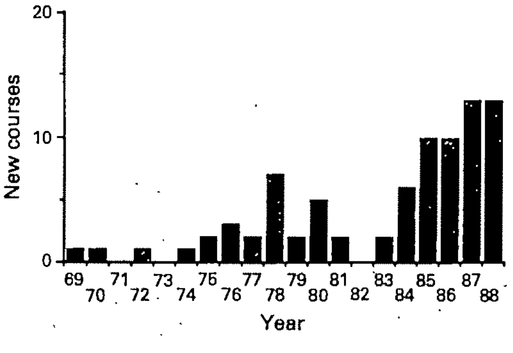

Figure 3 Number of new cardiac rehabilitation programmes established each year.

8 Comment on current provision

8.1 There is a striking lack of cardiac rehabilitation facilities in the British Isles at present, with large areas of the country offering no facilities at all. As a result the full benefit of the advances in medical and surgical treatment are not being realised. There is, however, a growing interest at "grass roots" level which may be stimulated by the recommendations made in the recent Royal College of Physicians report on Medical Aspects of Exercise.[36] In a recent survey by the Coronary Prevention

Group, about one third of Health Districts wished to establish a rehabilitation programme, and only one third expressed no interest.

8.2 The level of direct involvement by cardiologists in rehabilitation programmes in the British Isles is very low, with less than one third of established courses retaining the support of the local cardiologist. It is perhaps surprising that although most cardiologists make extensive use of exercise testing after myocardial infarction, so few use this to aid exercise training. This may reflect the current emphasis in training on "high tech" procedures rather than a more holistic approach to patient care. Nevertheless, the cardiologist will remain the most appropriate individual to co-ordinate the activities involved in cardiac rehabilitation in most district hospitals.

8.3 The role of cardiac rehabilitation after myocardial infarction and coronary artery bypass graft surgery is generally established, but patients also benefit after cardiac transplantation or valve surgery. Rehabilitation may also be beneficial for patients with angina pectoris who have not yet sustained a myocardial infarction, patients with class II or III heart failure, after angioplasty, physiological pacemaker implantation, and prosthetic valve surgery; and in younger patients after correction of congenital heart lesions. The disparate nature of these groups emphasises the importance of tailoring programmes to individual patient needs; congenital heart disease patients and prosthetic valve recipients may well benefit from the non-exercise elements of cardiac rehabilitation.

8.4 Many programmes tend only to include patients up to the age of 65 and it is now generally agreed that there should be no specific age limit; elements of the rehabilitation programme applicable to patients in the older age groups should be made available.

8.5 The lower incidence of coronary heart disease in women has led to fewer female patients being included in programmes. Though a training response similar to that in men can be obtained, drop-out rates are high both in the British Isles[37] and the United States.[38] Therefore, female patients need to be encouraged to participate in rehabilitation particularly because the psychological and vocational aspects of cardiac disease in women has attracted insufficient attention.

8.6 Perhaps because of the pressures under which many programmes operate, little attention is given to the non-attender. Such patients frequently have social or psychological problems that place them in a high risk group. The rehabilitation co-ordinator is probably best placed to identify problems that may prevent patients attending and bring them to the attention of the clinician concerned.

8.7 If cardiac rehabilitation is to fulfil a long-term preventive function there must be more emphasis on continuing exercise and risk factor modification as seen in North America and Europe. This is only feasible on any scale in the British Isles with self-help groups, often supported by charities such as the Chest Heart and Stroke Association. At present these facilities exist in less than 20% of health districts. Medical risk factors such as hypertension and hyperlipidaemia are the responsibility of the primary health care team.

9 Recommendations

9.1 Every major district hospital that treats patients with heart disease should provide a cardiac rehabilitation service; at present too few do.

9.2 The programme should be multidisciplinary and usually exercise based, depending on the resources available. A local co-ordinator is essential.

9.3 The expertise available for a comprehensive programme is available in most district and major cardiothoracic centres, but requires consultant leadership, most appropriately by a cardiologist.

9.4 There is a continued need for research into the evaluation of not only the physiological response, but also the social and psychological aspects of rehabilitation.

9.5 The role of vocational rehabilitation in recovery needs greater recognition.

9.6 The special problems of women and children and certain ethnic groups need to be addressed.

9.7 Rehabilitation should be tailored to the individual needs of patients and special group requirements. Arrhythmia monitoring is necessary for high risk patients.

9.8 Individual programmes should evaluate their outcome, and a standard format of audit could be agreed nationally to allow comparison.

1 Chapman CB, Fraser RS. Studies on the effect of exercise on cardiovascular function III. Cardiovascular response to exercise in patients with healed myocardial infarction. *Circulation* 1954;**9**:347–51.

2 Kellermann JJ, Levy M, Feldman S, Kariv I. Rehabilitation of coronary patients. *J Chronic Dis* 1967;**20**:815–21.

3 Brunner D. Active exercise for coronary patients. *Rehabilitation Record* 1968;**9**:29–31.

4 Gottheiner V. Long range strenuous sports training for cardiac reconditioning and rehabilitation. *Am J Cardiol* 1968;**22**:426–35.

5 Hellerstein HK, Ford AB. Rehabilitation of the cardiac patient. *JAMA* 1957;**164**:225–31.

6 Zohman LR, Tobis JS. The effect of exercise training on patients with angina pectoris. *Arch Phys Med Rehabil* 1967;**48**:525–32.

7 Rechnitzer PA, Yuhasz MS, Paivio A, Pickard HA, Lefcoe N. Effects of a 24 week exercise programme on normal adults and patients with previous myocardial infarction. *Br Med J* 1967;i:734–5.

8 Varnauskas E, Bergman H, Houk P, Bjorntrop P. Haemodynamic effects of physical training in coronary patients. *Lancet* 1966;ii:8–12.

9 Clausen JP, Larson OA, Trap-Jensen J. Physical training in the management of coronary artery disease. *Circulation* 1969;**40**:143–54.

10 Lamm G, Denolin H, Duross EVD, Pisa Z. Rehabilitation and secondary prevention in patients after acute myocardial infarction. WHO collaborative study. *Adv Cardiol* 1982;**31**:107–11.

11 Morris JN, Heady JA, Raffle PAB, *et al.* Coronary heart disease and physical activity of work. *Lancet* 1953;ii: 1053–7 and 1111–20.

12 Paffenbarger RS, Hyde RT, Wing AL, Steinmetz CH. A natural history of athleticism and cardiovascular health. *JAMA* 1984;**252**:491–5.

13 Blair SN, Kohl HW, Paffenberger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness in all-cause mortality: A prospective study of healthy men and women. *JAMA* 1989;**262**:2395–401.

14 O'Connor GT, Buring JE, Yusuf S, Joldhager SZ, Olmstead EM, Paffenbarger RS, Hennekens CH. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;**80**:234–44.

15 Oldridge NB, Guyatt GH, Fischer MD, Rimm AA. Cardiac rehabilitation after myocardial infarction: Combined experience of randomized clinical trials. *JAMA* 1988;

260:945–50.

16 Clausen JP. Circulatory adjustments in dynamic exercise and effective physical training in normal subjects on patients with coronary artery disease. *Prog Cardiovasc Dis* 1976;18:459–95.

17 Paterson D, Shephard R, Cunningham D, Jones N, Andrew G. Effects of physical training on cardiovascular function following myocardial infarction. *J Appl Physiol* 1979; 47:482–99.

18 Williams R, McKinnis R, Cobb F, Higginbotham M, Wallace A, Coleman R, Califf R. Effects of physical conditioning on left ventricular ejection fraction in patients with coronary artery disease. *Circulation* 1984; 70:69–73.

19 Ehsani AA, Biello DR, Schultz J, Sobel BE, Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986;74:350–8.

20 Martin W, Heath G, Coyle E, Bloomfield S, Holloszy J, Ehsani A. Effect of prolonged intense endurance training on systolic time intervals in patients with coronary artery disease. *Am Heart J* 1984;107:75–81.

21 Ehsani A, Heath G, Hagberg J, Sobel B, Holloszy J. Effects of 12 months of intense exercise training on ischaemic S-T segment depression in patients with coronary artery disease. *Circulation* 1981;64:1116–24.

22 Ghilarducci LE, Holly RG, Amsterdam EA. The effects of high resistance training in coronary artery disease. *Am J Cardiol* 1989;64:866–70.

23 Wenger MK, Hellerstein HK, Blackburn H, Castranova SJ. Physician practice in the management of patients with uncomplicated myocardial infarction; changes in the past decade. *Circulation* 1982;65:421–7.

24 Collins R, Yusuf S, Peto R. Exercise after myocardial infarction reduces mortality: Evidence of randomized control trial (RCTs) [abstract]. *J Am Coll Cardiol* 1984; 3:622.

25 Coats AJS, Adamopoulos S, Meyer TE, Conway J, Sleight P. The effects of physical training in chronic heart failure. *Lancet* 1990;335:63–6.

26 Kavanagh T, Yacoub MH, Mertens DJ, Kennedy J, Campbell RB, Sawyer P. Cardiorespiratory responses to exercise training after orthoptic cardiac transplantation. *Circulation* 1988;77:162–71.

27 Goble AJ, Adey GM, Bullen JF. Rehabilitation of the cardiac patient. *Med J Aust* 1963;2:975–82.

28 Mayou RA, Foster A, Williamson R. Psychosocial adjustment of patients one year after myocardial infarction. *J Psychosom Res* 1978;22:447–53.

29 Gundle MJ, Reeves BR, Tate S, Raft D, McLauren JP. Psychosocial outcome after coronary artery surgery. *Am J Psychiat* 1980;137:1591–4.

30 McHenry PL, Ellestad MH, Fletcher GP, Froelicher V, Hartley H, Mitchell JM, Froelicher ES. Statement on exercise. *Circulation* 1990;81:396–8.

31 Denolin H, Ferulilo GA, Gobbato F, Maisano G. Guidelines for return to work after myocardial infarction and/or revascularization. *Eur Heart J* 1988;9(suppl L):130–1.

32 Cardiac Rehabilitation Services. Health and Public Policy Committee, American College of Physicians. *Ann Intern Med* 1988;109:671–3.

33 Haskell WL. Cardiovascular complications during exercise training for cardiac patients. *Circulation* 1978;57:920–4.

34 Van Camp SP, Peterson RA. Cardiovascular complications of out-patient cardiac rehabilitation programmes. *JAMA* 1986;256:1160–3.

35 De Busk R, Haskell W, Miller N, Berra K, Taylor CB. Medically directed at-home rehabilitation soon after uncomplicated myocardial infarction: A new model for patient care. *Am J Cardiol* 1985;55:251–7.

36 Working Party Royal College of Physicians. Medical Aspects of Exercise Benefits and Risks. Summary of a report of the Royal College of Physicians. *J Royal Coll Phys Lond* 1991;25:193–6.

37 O'Callaghan WG, Teo KK, O'Riordan J, Webb H, Dolphin T, Horgan JH. Comparative response of male and female patients with coronary artery disease to exercise rehabilitation. *Eur Heart J* 1984;5:649–51.

38 Oldridge NB, Lasalle D, Jones NL. Exercise rehabilitation of female patients with coronary artery disease. *Am Heart J* 1980;100:755–7.

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Immunoglobulin response to intravenous streptokinase in acute myocardial infarction

SIR,—Lynch *et al*'s study (*British Heart Journal* 1991;**66**:139–42) contributes to the growing body of information on the immune response after administration of intravenous streptokinase for acute myocardial infarction. The current focus has been on the length of the period during which important titres of antibodies to and neutralising capacity for streptokinase persist (these do not always correlate precisely[2]). Studies by Lynch *et al*[1] and Jalilal and Morris[3] showed that this period extends at least to 12 months, and further work is awaited to determine the outer limit of this period. During this period streptokinase should not be readministered because of fears of an anaphylactic reaction and also that the drug will be neutralised and hence ineffective.

The current recommendations of the *1990–91 Data Sheet Compendium* are that a second dose of streptokinase should not be given within a period of five days to six months after the first. A recent *Drug and Therapeutics Bulletin* states that this will soon be amended to a 12 month interval.[4] Recent authoritative papers[5 6] have been broader in their recommendations, suggesting that streptokinase and anistreplase should not be readministered within a year, and the latter paper[6] concluded with the assertion that tissue plasminogen activator (alteplase) should be used if repeat thrombolysis is required (no time limit was stated so it presumably extended indefinitely from day 0). A policy of not repeating streptokinase for a year from day 0 has been widely adopted. These conclusions are important because alteplase costs ten times as much as streptokinase.

This policy loses sight of the early window that exists before the development of a significant immune response to streptokinase. This is a worthwhile opportunity given that 9% of patients will reinfarct in the first year after thrombolysis.[7] In a substantial number of these patients reinfarction requiring repeat thrombolysis occurs in the first few days after thrombolysis. In White *et al*'s 1990 study of repeat thrombolysis after myocardial infarction 31 patients were treated for recurrent myocardial infarction after thrombolysis between one and 716 days after initial thrombolysis.[5] The median interval was only five days and 10 of the 31 patients were treated in the first three days. Lynch *et al*'s study shows that antibody titres to streptokinase (IgG) do not rise above baseline until day four, suggesting that a significant immune response (either anaphylactic or neutralising) is unlikely before this. The work of Massel *et al* on neutralising antibody showed a neutralising capacity equivalent to $1·5 \times 10^6$ units streptokinase between days five and nine in all their patients[8] (this small study (11 patients) may not have adequately defined the normal range). This again suggests that there is an early opportunity to readminister streptokinase safely and effectively. Indeed though White *et al* recommended that streptokinase should not be readministered within a year they did show that readministration within this period was effective (albeit with an increased incidence of minor side effects).

This evidence suggests that streptokinase can be readministered safely and effectively from 0 to 3 days after the initial event. A further large study of neutralising capacity would be helpful because the most recent study dealt only with antibody response and a previous study of neutralising capacity was small. If this policy is adopted as a refinement of the day 0 to one year policy, which seems to be emerging, it is likely to have an impact on coronary care unit drug bills.

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1 Lynch M, Littler WA, Pentecost BL, Stockley RA. Immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;**66**:139–42.
2 Moran DM, Standring R, Lavender EA, Harris GS. Assessment of anti-streptokinase antibody levels in human sera using a microradioimmunassay procedure. *Thromb Haemost* 1984;**52**:281–7.
3 Jalilal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; **335**:184–5.
4 *Drug Ther Bull* 1991;**29**:16.
5 White HD, Cross DB, Williams BF, Norris RM. Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction. *Br Heart J* 1990;**64**:177–81.
6 White H. Thrombolytic treatment for recurrent myocardial infarction. *BMJ* 1991;**302**: 429–30.
7 Rivers JT, White HD, Cross DB, Williams BF, Norris RM. Reinfarction after thrombolytic therapy for acute myocardial infarction followed by conservative management: incidence and effects of smoking. *J Am Coll Cardiol* 1990;**16**:340–8.
8 Massel D, Turpie AGG, Gill JB, Cairns JA, Russett J. Development of neutralizing antibodies after 1·5 million units of streptokinase in the treatment of acute myocardial infarction [abstract]. *Circulation* 1989; **80**(suppl II):350.

This letter was shown to the authors and an advisor, who reply as follows:

SIR,—We are grateful to Dr Grant for his comments. We agree, as stated in our final paragraph, that it would be prudent to avoid repeating the dose between three days and at least one year after the initial treatment with streptokinase. After treatment with streptokinase, the antibody titre (IgG, subclass IgGI) virtually disappears, presumably because the antibody combines with the antigen, streptokinase. Subsequently, there is a gradual rise in antibody titre, which does not become significantly higher than baseline titres until day 4. During this time window of 0–3 days, when antibody titres are no higher than pretreatment titres, it is probably as safe and effective to re-administer streptokinase in the event of a repeat infarction as in the case of the initial infarct.

We are continuing to monitor streptokinase antibody titres in this cohort of 20 patients, who have now reached the 18 month time point. Though they are gradually declining, the mean (SD) IgG titres to streptokinase are still significantly raised at two years (86·42 (102·9)) over baseline titres (14·63 (4)) ($p < 0·025$). Repeat infarction after 72 hours and until at least 18 months after the initial infarct should probably be managed with a non-streptokinase thrombolytic agent until the significance of these antibodies is known.

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SIR,—Dr Grant raises an interesting point about the possible readministration of streptokinase or streptokinase-containing compounds in the first three days after initial administration. Specific antistreptokinase IgG concentrations initially fall and then increase over this time[1] and there may be an early time window when readministration could be safe and effective. However, the time course of the immunological response varies from patient to patient and individual patients may therefore receive ineffective therapy if this approach is adopted.

Readministration of *effective* thrombolytic therapy is important because reocclusion in the first few days is associated with poor clinical outcome and higher mortality. For example, in the TAMI (thrombolysis and angioplasty in myocardial infarction) trials patients who had an initially patent artery that then reoccluded over the first few days had a significant increase in hospital mortality from 4·5% to 11% ($p = 0·01$).[2]

Other thrombolytic agents available such as urokinase or alteplase can be used without raising concern about the effectiveness of readministration. It seems prudent, therefore, not to readminister streptokinase or compounds containing streptokinase in the first few days unless evidence emerges that high titres of antistreptokinase IgG or high neutralisation titres do not compromise safety or efficacy.

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2 Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R, and the TAMI study group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;**82**:781–91.

Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease

SIR,—McCance and Forfar (*British Heart Journal* 1991;**66**:316–9) reported the effects of adrenaline on the development of ischaemia and arrhythmia in patients with ischaemic heart disease.[1] One of their principal findings was that adrenaline produced ischaemia at a lower rate-pressure product than exercise. This raises many important questions about the mechanisms through which catecholamines produce ischaemia and about how such ischaemia can be prevented.

McCance and Forfar postulate that redistribution of coronary flow is the mechanism underlying the greater ischaemic effect of adrenaline, but recent biochemical data suggest an alternative explanation. Adrenaline (released from the adrenal medulla during stress) is a more potent stimulator of the β-2 subtype of adrenoreceptor than noradrenaline (released from the sympathetic nerve endings during exercise). Stimulation of cardiac β-2 adrenoreceptors, like β-1 adrenoreceptors, has positive inotropic and chronotropic effects.[2,3] However, biochemical studies have shown important differences in the linkage of β adrenoreceptor subtypes to cardiac adenylate cyclase, with a higher proportion being linked to β-2 adrenoreceptors than to β-1 adrenoreceptors.[4] Not all adenylate cyclase when activated leads to increased contractility; therefore, adrenaline activation of adenylate cyclase not linked to contraction (possibly linked to metabolic pathways) may lead to a further increase in oxygen consumption. This differential coupling to adenylate cyclase may explain why adrenaline infusions produce greater ischaemia than exercise for a given rate-pressure product.

Whatever the underlying mechanism, this study has important therapeutic implications. By failing to block β-2 adrenoreceptors selective β-1 blockade will be inferior to non-selective β-blockade at antagonising the effects of adrenaline. Additionally selective β-1 blockade may actually lead to an enhancement of the ischaemic and arrhythmogenic effects of adrenaline because β-1 blocker treatment leads to a selective enhancement of the sensitivity of the heart to β-2 adrenoreceptor stimulation.[5-7] This may have enhanced the differences between exercise and adrenaline infusion seen in McCance and Forfar's study since 13/14 patients were taking a β-1 selective blocker (atenolol, metoprolol, and bisoprolol) until a few days before the study. Therefore this study adds further weight to the argument that non-selective β blockade may have advantages over β-1 selective blockade during stress—for example, myocardial infarction.

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1 McCance AJ, Forfar JC. Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease. *Br Heart J* 1991;66:316–9.
2 Kaumann AJ, Lemoine H. β-2 adrenoreceptor mediated positive inotropic effect of adrenaline in human ventricular myocardium. *Naunyn-Schiedebergs Arch Pharmacol* 1987;335:403–11.
3 Hall JA, Petch MC, Brown MJ. Intracoronary injections of salbutamol demonstrate the presence of functional β-2 adrenoreceptors in the human heart. *Circ Res* 1989;65:546–53.
4 Kaumann AJ, Hall JA, Murray KJ, Wells FC, Brown MJ. A comparison of the effects of adrenaline and noradrenaline on human heart: the role of β-1 and β-2 adrenoreceptors in the stimulation of adenylate cyclase and contractile force. *Eur Heart J* 1988;10(suppl B):29–37.
5 Hall JA, Kaumann AJ, Brown MJ. Selective β-1 adrenoreceptor blockade enhances positive inotropic responses to endogenous catecholamines mediated through β-2 adrenoreceptors in human atrial myocardium. *Circ Res* 1990;66:1610–23.
6 Hall JA, Petch MC, Brown MJ. In vivo evidence of cardiac β-2 adrenoreceptor sensitisation due to atenolol treatment. *Circ Res* 1991;69:959–64.
7 Ferro A, Hall JA, Brown MJ. Selective potentiation of cardiac β-2 responses caused by β-1 blockade with bisoprolol 1991. *Clin Sci* 1991;81(suppl 25):16.

This letter was shown to the authors who reply as follows:

Sir,—We thank Hall and Ferro for their interesting comments on our paper. The mechanism of our observation that adrenaline produced ischaemia at a lower rate-pressure product than exercise must remain speculative, but we agree that the mechanism proposed by Hall and Ferro is also consistent with our data.

It is interesting to consider the ideal properties for a β blocker in the setting of acute myocardial infarction. The beta-1 selective agent atenolol was shown in ISIS-1[1] to reduce mortality when used early in acute myocardial infarction, a benefit largely due to a decrease in cardiac rupture. No other β blocker has been shown to decrease mortality when given acutely. But both propranolol[2] and metoprolol[3] have been shown to reduce ventricular fibrillation in acute myocardial infarction. In animal studies timolol, pindolol, propranolol, metoprolol, and labetalol all increased the ventricular fibrillation threshold to a similar extent.[4]

Adrenaline is unlikely to be of direct relevance in causing late mortality after acute myocardial infarction but the question of which β blocker to use orally *after* acute myocardial infarction is as important as the question of which β blocker to use acutely. Propranolol, timolol, and metoprolol are all reported to reduce mortality and particularly sudden death after acute infarction.[5] The mechanisms of benefit may be many and are probably different from those when β blockers are used acutely.[6] It may be that here lipid solubility is more important than β-1 selectivity. An overview of the long-term β blocker trials has not suggested any difference between the β-1 selective and non-selective β blockers,[7] though it seems that β blockers that do not have partial agonist activity may be more effective than those that do. There are insufficient data to be certain whether lipid solubility is important in this respect but all the drugs known to be efficacious are lipid soluble. Given the uncertainty about the importance of the ancillary properties of β blockers it seems reasonable to suggest that only β blockers with proven effects should be used for postinfarction prophylaxis[5] and, despite the theoretical advantages of non-selective β blockade advanced by Hall and Ferro, the same is probably true of the use of intravenous β blockade in acute infarction. Thus we believe that, in the absence of proof of the relative benefits of non-selective and selective β blockers, atenolol and possibly metoprolol should remain for the present the first line intravenous β blockers in acute myocardial infarction.

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1 ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. *Lancet* 1986;ii:57–66.
2 Norris RN, Barnaby PF, Brown MA, Geary GG, Clarke ED, Logan RL. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. *Lancet* 1984;ii:883–6.
3 Reiden L, Ariniego R, Amman K, *et al.* A double-blind trial of metoprolol in acute myocardial infarction: Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983;308:614–8.
4 Anderson JL, Rodier HB, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol* 1983;51:1196–202.
5 Hjalmarson A, Olsson G. Myocardial infarction: Effects of β-blockade. *Circulation* 1991;84(suppl VI):101–7.
6 Ollson G, Ryden L. Prevention of sudden death using β-blockers: Review of possible contributory actions. *Circulation* 1991;84(suppl VI):33–7.
7 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985;27:335–71.

Cyclosporin treatment and nitric oxide release in human coronary arteries

Sir,—We read with interest the report by Dr O'Neil and colleagues (*British Heart Journal* 1991;66:212–6) of the lack of effect of cyclosporin on nitric oxide release in human coronary arteries.[1] The data they presented are most valuable because they were obtained from human studies. However, we feel that the conclusion of the paper should be re-examined in the light of their results.

To assess the effect of cyclosporin in vitro, O'Neil *et al* applied the protocol that we have previously described.[2] After three hours of incubation with cyclosporin, the maximal relaxation (mean (SEM)) to substance P was reduced from 76·6 (7·4)% in control coronary artery rings to 63·0 (11·5)% and 62·2 (11·1)% in rings pretreated with cyclosporin 1000 and 2000 ng/ml, respectively. This difference was not statistically significant. However, at lower concentrations (10^{-10} and 10^{-9} mol/l) of substance P, the relaxant responses were significantly reduced in coronary artery rings incubated with cyclosporin compared with control rings (shown by O'Neil *et al* in fig 1). Substance P is known as an endothelium-dependent vasodilator[3] and has already been used by O'Neil *et al* to test the ability of the coronary circulation to release nitric oxide in vitro in humans.[4] As with other human vascular diseases,[5,6] the mechanisms for relaxation of the underlying vascular smooth muscle in response to nitrovasodilators were not affected by cyclosporin (shown by O'Neil *et al* in fig 2). We therefore cannot see any other interpretation than the one suggesting that nitric oxide release is indeed impaired in rings incubated with cyclosporin when tested with low concentrations (10^{-10} and 10^{-9} mol/l) of substance P. Usually when they find no statistical difference between the maximal responses of the rings workers calculate the dose of agonist eliciting 50% of the full response (EC_{50}). This universally accepted method allows the detection of any shift of the dose-response curves. Inspection of fig 1 indicates that there is indeed a rightward shift of the dose-response curves obtained from rings treated with cyclosporin in vitro.

O'Neil *et al* found no significant correlation between the in vivo and in vitro coronary vasodilatory responses to substance P with either blood concentration of cyclosporin (fig

4) or the duration of treatment (fig 3). However, the correlation made from the in vitro study was for data in only three patients.

No information was given as to the clinical status of the 12 patients studied in vivo, especially their vasodilator regimens, the frequency of episodes of rejection, the use of other immunosuppressive agents, etc . . . In patients with transplanted hearts the reactivity of any particular vascular bed is likely to be influenced by several interconnected factors. Therefore, the influence of a single factor, in this case cyclosporin treatment, cannot be assessed by simple linear regression. Furthermore, the study of the effect of cyclosporin on nitric oxide release after stimulation by substance P needs a control group. There was a control group in the in vitro study but not the in vivo study.

In conclusion, we applaud O'Neill *et al* for their effort to address the important issue of vascular toxicity of cyclosporin in patients with transplants. However, we feel that both the design and the results of the study do not quite support the clear cut conclusion they made.

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1 O'Neil GS, Chester AH, Kushwaka S, Rose M, Tadjkarimi S, Yacoub MH. Cyclosporin treatment does not impair the release of nitric oxide in human coronary arteries. *Br Heart J* 1991;66:212–6.
2 Dinh-Xuan AT, Fan TPD, Higenbottam TW, Wallwork J. Cyclosporine in vitro reduces endothelium-dependent relaxation to acetylcholine but does not affect relaxation to nitrovasodilators. *Transplant Proc* 1990;22:1723–5.
3 Dinh-Xuan AT, Higenbottam TW. Non-prostanoid endothelium-derived vasoactive factors. *J Int Med Res* 1989;17:305–15.
4 Chester AH, O'Neil GS, Moncada S, Tadjkarimi S, Yacoub MH. Low basal and stimulated release of nitric oxide in atherosclerotic epicardial coronary arteries. *Lancet* 1990;336:897–900.
5 Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990;323:22–7.
6 Dinh-Xuan AT, Higenbottam TW, Clelland CA, *et al*. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991;324:1539–47.

This letter was shown to the authors, who reply as follows:

Sir,—We used three distinct models to assess the effect of cyclosporin on endothelial function in the human coronary circulation: none of them showed that cyclosporin was capable of compromising the ability of the vascular endothelium to release nitric oxide in response to an endothelium dependent vasodilator.

Dr Dinh-Xuan and Dr Higenbottam are correct in pointing out the importance of EC_{50} values in comparing the difference in the response to low concentrations of substance P. Calculation of the EC_{50} values shows minimal dose ratio shift of <3, but the maximum dilatory response was preserved. In our discussion we pointed out the loss in sensitivity at low concentrations of substance P, but we believe that in light of the evidence from the retransplanted patients and the in vivo study this effect is not clinically relevant. This view accords with the results from our previously published data where therapeutic concentrations of cyclosporin had no effect on any part of the dose response curve for substance P in human coronary arteries.[1]

We stated both in the abstract and the methods section that the patients in the in vivo study were clinically well and free of rejection at the time of assessment. Admittedly, these patients do form a complex group in terms of medication and clinical history. However, irrespective of "interconnected factors" the fact remains that patients who receive cyclosporin after transplantation, retain a response to substance P and isosorbide dinitrate that resembles that reported in healthy volunteers.[2]

Data from human studies are important in that a previous report by Dinh-Xuan *et al*[3] suggests that inhibition of the release of endothelium dependent relaxing factor (EDRF) in a rat model may contribute to the underlying mechanisms of cyclosporin associated hypertension in humans. We attribute this to a genuine species difference, however, it seems that from the most recent reports the cyclosporin associated vascular dysfunction in rat aortae may also be due to an increased response to vasoconstrictors rather than to a reduction in EDRF release.[4]

The mechanisms underlying the vascular effects of cyclosporin in humans that precipitate clinically relevant hypertension and renal damage remain to be elucidated. Our findings indicate that direct inhibition of nitric oxide is unlikely to be the mechanism responsible.

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1 O'Neil GS, Chester AH, Rose M, Tadjkarimi S, Yacoub MH. The effect of cyclosporine on the release of endothelium-derived relaxing factor from isolated human epicardial coronary arteries. *Transplantation* 1991;51:736–8.
2 Crossman DC, Larkin SW, Fuller RW, Davies GJ, Maseri A. Substance P dilates epicardial coronary arteries and increases blood flow in humans. *Circulation* 1989;80:475–84.
3 Dinh-Xuan AT, Fan TPD, Higenbottam TW, Wallwork J. Cyclosporine in vitro reduces endothelium-dependent relaxation to acetylcholine but does not affect relaxation to nitrovasodilators. *Transplant Proc* 1990;22:1723–5.
4 Chan BBK, Kern JA, Flanagan TL, Tribble CG, Kron IL. Effects of cyclosporine A (CSA) on vascular endothelial function and morphology. *Circulation* 1991;(suppl II),84:492.

Antihypertensive drugs and plasma lipids

Sir,—In his editorial (*British Heart Journal* 1991;66:409–10) Professor Swales commented that a trial comparing diuretics or β blockers with one of the new classes of agents would be desirable. He also writes that "such an end point trial has not been set up and it is unlikely to be set up in the near future . . ." The Captopril Prevention Project (CAPPP), which is now in its second year and conducted with the endorsement of the European Society of Hypertension, is precisely such a trial. Its aims and design have been reported.[1] In brief, hypertensive men and women aged 25–66 are randomised to captopril based treatment or diuretic β blocker based treatment (ACE inhibitors excluded); the aim is to detect a 20% difference in cardiovascular mortality with a power of 80% at the 5% significance level (two sided).

The study is being conducted at 275 health care centres in Sweden and Finland and the PROBE (prospective, randomised, open, blinded end point evaluation) design is used.[2] In September 1991 more than 6000 patients had been recruited to CAPPP. It is hoped that by 1996 enough end points will have accumulated for the study to be ended (with a significant outome).

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1 The CAPPP Group. The Captopril Prevention Project: a prospective intervention trial of angiotensin converting enzyme inhibition in the treatment of hypertension. *J Hypertens* 1990;8:985–90.
2 Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Pressure* (in press).

Avoidance of tolerance and lack of rebound with intermittent dose titrated transdermal glyceryl trinitrate

Sir,—The study by Fox *et al* (*British Heart Journal* 1991;66:151–5) addressed an important question concerning nitrate tolerance and "rebound angina" during nitrate free periods. However, the main conclusions of the study are neither new nor entirely accurate, and leave many questions unanswered. How long do the patches remain effective? Do they last all day? When does tolerance start to develop and how long a nitrate free period is required to prevent the development of tolerance? "Rebound" might not be such a problem if the patches only need to be left off for an hour or two.

At least five previous studies have now shown that nitrate patches remain effective shortly after being re-applied after a nocturnal nitrate free period. What remains unclear, however, is how quickly tolerance develops after a patch has been applied, and therefore what is the duration of daytime efficacy during an intermittent treatment regimen. It is also not known how long a nitrate free period is required to reverse tolerance; this study does nothing to address these points.

We examined many of these questions in a previous study (the results of which were presented to the British Cardiac Society in 1987).[1] Using three active or dummy patches applied consecutively for 32–36 hours and conduction of four exercise tests over this period we assessed the effects of continuous treatment for three, eight, 12, 15, and 24 hours, and of intermittent treatment on two consecutive days using two different nitrate free periods of 12 or 16 hours. Our results showed the now familiar finding that the patches remained effective three hours after treatment was restarted.[2] They also showed that the length of nitrate free interval (12 hours or 16 hours) did not influence this response. However, rather more important was the finding that whatever the length of the nitrate free interval the therapeutic effects became somewhat attenuated within eight hours of the start of treatment and appreciably so after 12 hours: there was therefore no point in testing a shorter nitrate free interval because important therapeutic effects do not seem to last for over 12 hours of continuous therapy. Waters *et al* were also unable to show therapeutic benefit during intermittent treatment when they tested 12 and 16 hours after patch application[3] and though Schaer *et al*[4] showed significant effects at four and eight hours it was clear from inspecting their data that the results at eight hours were rather less statistically significant than those at four hours. It thus seems likely that tolerance develops so quickly during transdermal therapy that it limits its efficacy as a day long prophylactic agent.

The study reported by Fox *et al* rather supports our findings because treatment had very little influence on the circadian pattern of silent ischaemia—as one would expect if treatment had only been effective during the first few hours.

It is certainly not justified to conclude that the significant treatment effects demonstrated between three and five hours after patch application indicate that tolerance has been "avoided". Our results supported by data from other studies suggest that while the effects measured at 3–5 hours may have remained significantly better than those seen during placebo treatment, they are likely to be significantly worse than those seen after only 30–60 minutes of treatment and significantly better than those measured after eight hours or more. In other words, it seems likely that tolerance is a gradual but continuous process beginning from the moment that treatment is initiated.

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1 James MA, Papouchado M, Jones JV. Tolerance to nitrates: does it occur and how long a nitrate free period is required to prevent it? [abstract]. *Br Heart J* 1988;59:125.
2 James MA, Papouchado M, Jones JV. Attenuation of nitrate effect during an intermittent treatment regimen and the time course of nitrate tolerance. *Eur Heart J* 1991;12: 1266–72.
3 Waters DD, Juneau M, Gossard D, Choquette G, Brien M. Limited usefulness of intermittent nitroglycerin patches in stable angina. *J Am Coll Cardiol* 1989;13:421–5.
4 Schaer DH, Buff LA, Katz RJ. Sustained antianginal efficacy of trans-dermal nitroglycerin patches using an overnight 10 hour nitrate free interval. *Am J Cardiol* 1988;61:46–50.

Novel exercise protocol suitable for use on a treadmill or a bicycle ergometer

SIR,—In their letter Dr Essamri and colleagues correctly state that the standardisation of exercise tests is now a major issue (*British Heart Journal* 1991;66:405–6) but they criticise the standardised exponential exercise protocol (STEEP) devised by Dr Northridge and colleagues (*British Heart Journal* 1990;64:313–6). In this useful protocol the exponential increase in work rate tends to keep exercise duration within the "ideal" range of 5–15 minutes even if exercise capacity in terms of peak external work rate differs widely. Detailed tables are provided for cycle ergometry work rates adjusted for the subject's weight so that their STEEP will be similar on a cycle ergometer and on a treadmill.

The differences between the cycle ergometer STEEP and treadmill STEEP protocols reported by Dr Essamri are relatively small—approximately a 13–19% difference in $\dot{V}O_2$ over the last six minutes of exercise. Such differences are expected because the cardiopulmonary responses to exercise vary according to the mass of active muscle: at a given submaximal work rate, heart rate and $\dot{V}O_2$ tend to be higher with cycle ergometry, whereas peak heart rate and $\dot{V}O_2$max tend to be higher on treadmill exercise.[1,2] Standardisation of work rate according to lean body mass rather than total body weight might further reduce these differences,[3,4] but to expect cycle ergometry and a motorised treadmill to be equivalent is unrealistic.

Dr Essamri and collegues also suggest that the relatively slow rise in $\dot{V}O_2$ over the first minutes of the STEEP makes it an unsuitable basis for the prediction of $\dot{V}O_2$max from $\dot{V}O_2$ at submaximal work rates. However, such extrapolations are always subject to large errors[5,6] and maximal tests are preferred when $\dot{V}O_2$max is to be determined.[7]

However, in the graphs presented by Dr Northridge and Dr Essamri we note that $\dot{V}O_2$ continues to increase steeply as a function of time over the last few minutes of exercise, whereas in many other protocols $\dot{V}O_2$ tends towards a plateau—it rarely if ever attains a plateau but at least becomes less steep, with a negative second derivative $d^2\dot{V}O_2/d\,(\text{time})$.[2] If subjects perform maximal symptom limited exercise then the effect of the continued steep rise in $\dot{V}O_2$ may be to amplify the effects on measured $\dot{V}O_2$peak of small changes in exercise duration due to variations in motivation and encouragement.

The debate between proponents of the cycle ergometer and proponents of the motorised treadmill is likely to continue for many years—the advantages and disadvantages of each are balanced and preferences often differ on a geographical basis.[8,9] As it is unlikely that cardiologists in all countries will agree to standardise on one or other form of exercise testing, the STEEP is a useful attempt to bridge this divide.

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2 Martin WH III, Berman WI, Buckey JC, Snell PG, Blomqvist G. Effects of active muscle mass size on cardiopulmonary responses to exercise in congestive heart failure. *J Am Coll Cardiol* 1989;14:683–94.
3 Jones NL. Clinical exercise testing, 3rd ed. Philadelphia: W B Saunders, 1988:160–1.
4 Sparling PB, Cureton KJ. Biological determinants of the sex difference in 12-minute run performance. *Med Sci Sports Exer* 1983; 15:218–23.
5 Astrand P-O, Rodahl K. Textbook of work physiology. 3rd ed. New York: McGraw-Hill, 1986:376.
6 Legge BJ, Banister EW. The Astrand-Ryhming nomogram revisited. *J Appl Physiol* 1986; 61:1203–9.
7 Jones NL. Clinical exercise testing. 3rd ed. Philadelphia: W B Saunders, 1988:127–8.
8 Atterhog J-H, Jonsson B, Samuelsson R. Exercise testing in Sweden: a survey of procedures. *Scand J Clin Lab Invest* 1979;39:87–92.
9 Stuart RJJ, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980; 77:94–7.

BOOK REVIEW

Cardiac Electrophysiology and Arrhythmias. Eds Charles Fisch, Borys Surawicz. (Pp 448; $84) New York: Elsevier, 1991. ISBN 0-444-01601-5

This book is in many ways a testimony to the extraordinary progress in the subject over the past two or three decades. Indeed, 30 years ago there would have been little worth writing save for the six chapters on clinical arrhythmias, and each of these is in any case substantially influenced by the advent of clinical electrophysiological studies.

The editors, two leaders in the field, and respected because they have proved themselves in the classic tradition over the years, are to be commended for the fact that they have broadened the scope so considerably beyond Fisch's own recent book on the electrocardiographic diagnosis of arrhythmias. The first two major parts include chapters on mechanisms and on experimental arrhythmias which some might, unwisely, decide to gloss over. Difficult though some may be for the clinician, they are well worth reading for they form the scaffolding upon which the edifice of clinical arrhythmias, their diagnosis and management, depend. Over the past 20 years we have all become aware of the importance of the cardiac action potential and of ion movements, both in the genesis of normal and abnormal rhythms and in consideration of their treatment in some instances. But no longer can one divide arrhythmias in an apparently simple fashion into those dependent on automaticity and those that arise because of reentry; one can get deeper, by looking into the factors that promote such changes and also give rise to afterdepolarisations, the relevance of which are now becoming better appreciated.

Many will turn first, and justifiably, to the two excellent chapters on the differential diagnosis of tachycardias dependent on the width of the QRS, by Fisch and by Wellens; but there is important information in all the other chapters on clinical arrhythmias, and many who read these chapters will thereby be reminded of difficult cases that perhaps "got away". The use of exercise testing, signal averaged electrocardiography, and programmed electrical stimulation are all well discussed in separate chapters. The pharmacological sections offer relatively less new information and the chapter on sudden cardiac death, in particular, is somewhat out of place under pharmacology and not of the same high quality as most of the other contributions. The last part, dealing with nonpharmacological treatment, with emphasis on developments in pacing and ablative techniques (both electrically based and surgical) is of great interest because there are many developments in this area that are insufficiently widely known and where more patients could receive help.

Virtually all the chapters are well and relevantly referenced and the book not only has current usefulness but will continue to be a reliable and substantial source of information for some years to come. Many cardiologisits will wish to acquire it themselves as well as to see it on departmental library shelves.

DENNIS M KRIKLER

The title reviewed here is available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

Br Heart J 1992;**67**:423–4

BRITISH CARDIAC SOCIETY NEWSLETTER

Senior registrar posts: false alarms

Considerable anxiety has been caused in four regions over the past 18 months as each received notification of a reduction in the number of senior registrar posts approved by the Joint Planning Advisory Committee (JPAC). Mersey was the first to be affected, and Yorkshire the most recent. In no case had any consultation taken place. The situation in Liverpool took months to resolve, and eventually a post was restored seemingly as a gesture of goodwill. But since then, the Manpower Division of the Department of Health has been able to identify the problem. These threatened reductions seem to have resulted from confusion centrally over posts in adult and paediatric cardiology. In the last round of JPAC reviews the paediatric cardiologists presented their evidence separately, though the numbers come from a common pool. The paperwork seems not to have been properly integrated. Our next submission will be a joint one, so confusion can be avoided. Meanwhile we hope that the source of the error—now identified—has been removed so that no more spurious cuts will be announced. This newsletter has been critical in the past of the Manpower Division where bureaucracy seemed sometimes to be the enemy of reason instead of its servant. But changes have occurred, and we now enjoy an excellent liaison similar to that which proved so helpful to all parties in the past.

Senior registrar posts: JPAC review

Readers of the newsletter will not need reminding of our belief that the numbers of senior registrars allocated to cardiology is inadequate. Recently several appointment committees have interviewed only one candidate for consultant posts. Within five years the number of consultant retirements will double, and we could face a disastrous shortage. Our request for an earlier JPAC review was rejected a year ago on the grounds that there would be no suitable opportunity. But now the urgency is better appreciated, and we have been promised a review in November 1992, over a year earlier than the provisional date we had been given earlier. We still face one problem that is not the fault of the Department of Health nor of JPAC. For manpower planning, paediatric cardiology is considered part of cardiology at senior registrar level, but as part of paediatrics at registrar grade. The potential for further confusion in the training programme is clear. We hope that colleagues—mostly paediatricians—who oppose any change can be persuaded that the two components of specialist training must not be separated in this way.

Senior registrar posts: part-time training

Another recurring theme in the newsletter has concerned the difficulties faced by all who wish to avail themselves of part-time training at senior registrar level—usually women, though not exclusively so. We have listed the steps that have to be taken (newsletter, August 1991). We have written to all regional health authorities asking for sympathetic consideration for applicants—and in most cases had helpful and encouraging replies. But we have been surprised by a seemingly immovable impediment faced recently by one trainee. A woman wishing to make a career in cardiology was aware of the long procedure needed at present to obtain a part-time training post—approximately a year. Wishing to avoid disruption of her training, she made an application a few months before she was due to marry. This was refused. Marriage, it seems can sometimes be grounds for part-time training after the event, but a *potential* change in domestic circumstances is not. Should we be surprised that the attrition rate is so great as women attempt to progress from house officer to consultant if they are treated so unsympathetically? Is there *really* a commitment to part-time training, or is it a matter of using words to mask inaction? Should a well-founded wish to do part-time training not be a valid enough reason for application? No one would choose this long path needlessly because it must be a potential disadvantage in further advancement. We must add, however, that the arrangements for part-time training of senior registrars is under review. We hope for changes.

A parliamentary select committee

Since the announcement of a date for the general election, politics and politicians have been in the news to the extent that most of us feel the need for a break. Nevertheless we wish to recount the experience of attending a parliamentary select committee at Westminster. It was fascinating and impressive. Andrew Henderson has written about it. "At the instigation of the Cardiac Group in Wales the Welsh Affairs Committee considered the provision of cardiac services in Wales on 18 December 1991. It took evidence from representatives of the specialty in Wales, from the Parliamentary Under-Secretary of State, from the Director of the National Health Service in Wales, and from the Chief Medical Officer. It has now published its report. The cardiologists and cardiac surgeons throughout Wales had expressed their concern at the continuing delays in providing the much needed expansion of cardiac services, identified in 1981 in a report on cardiothoracic services in Wales. Expansion was promised by the then secretary of state for Wales in 1984. Wales has had a relatively low resource base of one regional centre with capacity for 600 operations per year, together with the lowest relative provision of cardiologists in the United Kingdom and half of its district general hospitals without a physician trained in cardiology. Concern was heightened by uncertainties surrounding the "de-regionalisation" of cardiac services and of the National Health Service changes. The experience was interesting, not least as a result of being able to remain as observers after we had given our evidence. The questioning was direct, though always courteous. The chairman had done his home-work well. It should be recorded that the President of the British Cardiac Society acted as specialist adviser to the committee. The professional witnesses gave evidence in line with the recommendations of the Joint College's Fourth Report (*Br Heart J* 1992;**67**:106–16) (which is included with the select committee's report), while outlining the factual background relating to cardiac services in Wales and the history of official statements relating to its provision. The parliamentary under secretary of state took the opportunity to announce additional funding of £5m to expand facilities at the University Hospital of Wales to an annual surgical capacity of 800 operations, £1·5m to other district health authorities to purchase cardiac surgery elsewhere, £2·5m to complete the development of the paediatric cardiac unit, and an appraisal of the longer term options for the shortfall of 400 operations relative to the pre-existing Welsh Office annual target of 1200 per year. The salient points of the report were (*a*) to welcome the announcement of funds for the overdue (and long promised) increase in capacity at the University Hospital of Wales; (*b*) to underline the urgency of the appraisal for a further increase in surgery (already promised in 1989 by the then secretary of state), and to recommend that its terms of reference are restricted to the size and location of a second unit in South Wales (despite the parliamentary under secretary of state's comments that the appraisal should embrace whether or not a second unit was still needed); (*c*) to emphasise the need for a major increase in the number of angioplasties; (*d*) to conclude that a reduction in cardiovascular mortality might paradoxically increase the need for treatment; (*e*) to recommend closer communication between Welsh Office and professional practitioners in this field (Wales has had no regional health authority); (*b*) to emphasise the need to provide within the principality the necessary capacity for cardiac services for Wales; and (*g*) to recommend that steps be taken to ensure that all district general hospitals in Wales have at least one physician trained in cardiology. This was a useful exercise. We hope that it has raised political awareness of the very real shortfall which exists in Wales while recommending that is needed in terms of capital investment and staffing to bring it up at least to reasonable levels by current United Kingdom standards. The committee has the advantage of being all-party and its record should thus stand as a yardstick for future governments of whatever colour."

Hypertrophic Cardiomyopathy Association

We have had a letter from John Goodwin concerning the Hypertrophic Cardiomyopathy Association. "Readers may like to see again a note about the Association (*British Heart Journal* 1990;**64**:410). The organisation was set up by sufferers from hypertrophic cardiomyopathy in the interest of patients and their relatives. The role of the association is one of guidance and counselling to help patients to understand the disease, adapt their life styles appropriately, and to cope with the psychological and emotional burdens of a condition in which sudden death is a feature, especially in young people. The administration of the association is advised on medical and technical matters by a medical sub-committee chaired by myself. A network of cardiologists is being set up around the country to advise on diagnosis, treatment, and counselling of patients and their families. The medical sub-committee have developed written guidelines on the management of hypertrophic cardiomyopathy. In addition to explaining the disease, these guidelines emphasise the importance to patients and their relatives of discussing their condition fully with their medical advisors. Further information may be obtained from the Chairperson, Mrs C Biro (telephone 0923 896776), from the Vice President, Dr W J McKenna, Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, Tooting SW17 0RE, or from me (President), c/o National Forum for Coronary Heart Disease Prevention, Hamilton House, Mabledon Place, London WC1H 9TX".

Read codes

The Read codes (newsletter, September 1991) will become increasingly important, but so far we clinicians have not played a major role in their application to cardiology. This is essential if their potential value is to be realised, though the task will be time consuming and will require both knowledge and experience. We are fortunate that Dr Malcolm Towers has agreed to represent cardiology in the development of new codes. His work will be of inestimable value to the data monitoring committee, to the society, and to our specialty.

Harrogate and the media

Finally one last piece of news about the Harrogate meeting. As usual, the press will not be allowed into the sessions, but as last year we will have press briefings. Some speakers will be asked to attend and we hope that they will do so. The media wish to respond to public interest, and for our part important messages can be widely disseminated. A higher public profile for the society remains one of our objectives.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
9 Fitzroy Square,
London W1P 5AH

NOTICES

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing data for receipt of abstracts was 3 January.

* * *

Sara Thorne from the Royal London Hospital and Jonathen Swan from the Wyn Institute have both won **Bristol-Myers Squibb Cardiovascular Awards** which will start in July 1992.

* * *

The office of the **British Heart Journal** has moved to 9 Fitzroy Square, London W1P 5AH (telephone 071 383 4006: fax 071 388 0903).

The International Workshop on Angina Pectoris with Normal Coronary Arteriograms sponsored by the European Society of Cardiology will take place on 12 June 1992 at the Department of Cardiological Sciences, St George's Hospital Medical School. The workshop is organised by J C Kaski and W J McKenna and has 19 invited speakers. The following topics will also be briefly discussed—current concepts on pathogenesis; metabolic regulation of coronary blood flow; prognosis and treatment of patients with angina and normal coronary arteries; angina pectoris in the cardiomyopathies; and future avenues of research. Registration fee (£75 including lunch, cheque payable to Special Trustees Medical Centre A/c) should be sent to Jill Williams, Postgraduate Manager, St George's Hospital, Grosvenor Wing, Blackshaw Road, London SW17 0QT.

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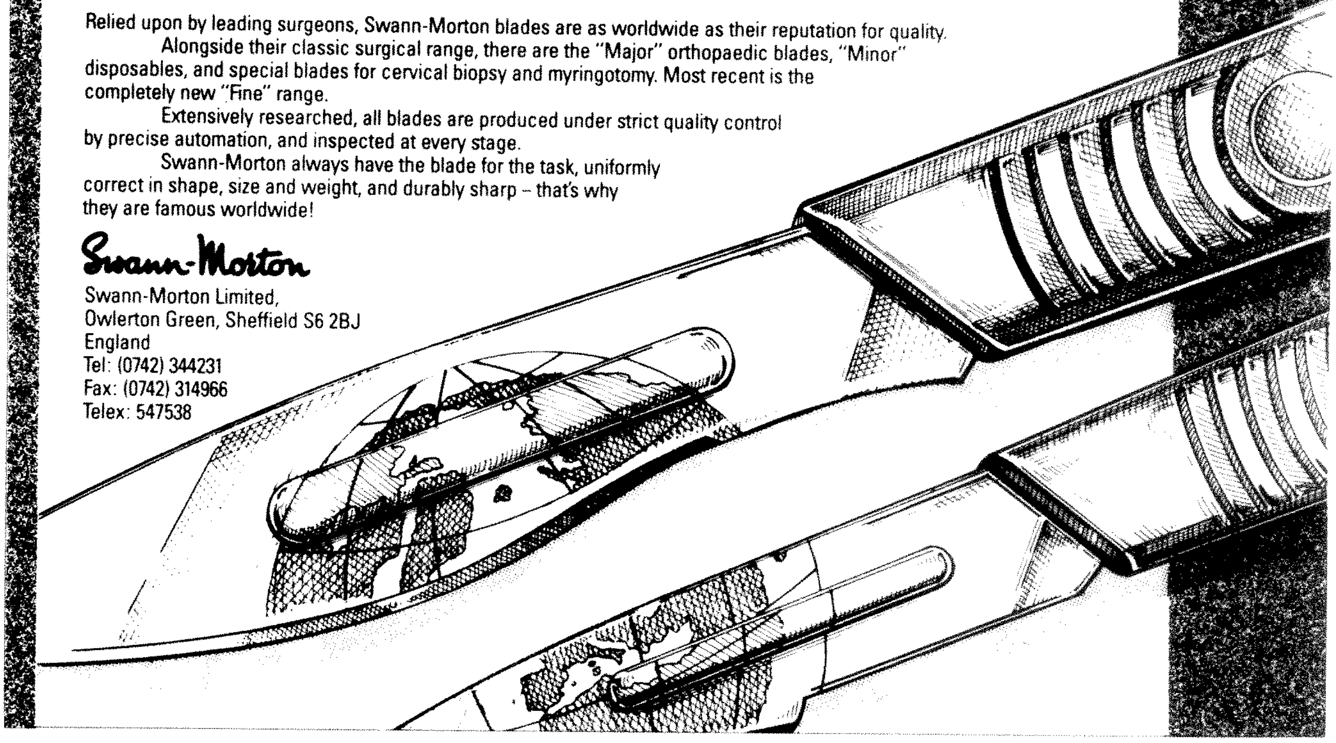

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Editorial

Intracoronary stents

The enormous growth of intracoronary interventions has brought an assortment of devices to help deal with coronary atheroma.[1,2] In most cases the clinical role of these devices has yet to be defined and reports of their benefits and complications are often confined to selected groups of patients. There is justifiable concern that the treatment may be worse than the disease[3] and that over-enthusiastic interventional cardiologists are modern "sorcerer's apprentices".[4]

In the November issue of the *British Heart Journal* Haude and colleagues reported their experience with the Palmaz-Schatz stent in 50 patients.[5] The indications included restenosis after a previous successful angioplasty, a poor angiographic result at the time of balloon angioplasty, "bail out" of coronary artery dissection and occlusion during angioplasty, and the treatment of stenoses in coronary vein grafts. Early events including death, need for bypass surgery, or stent thrombosis occurred in 10 patients, and bleeding complications in nine. In 41 patients angiographic follow up four to six months later showed restenosis or reocclusion in 10 (24%). Restenosis or late occlusion or both were more common in patients who received multiple stents.

These high rates of early thrombosis and of haemorrhage are similar to those reported in other series of coronary stents[6–9] and the overall restenosis rate is not much below that seen after conventional balloon angioplasty.[10–12] Despite this there is continuing interest in coronary stents because conventional balloon angioplasty is limited by the 5% incidence of acute dissection and occlusion of the coronary artery[13,14] and by the 30–40% incidence of angiographic restenosis.[10–12] In theory both these problems might be reduced by intracoronary stents if further research and development lead to improvements in stent materials and design.

Stents for "bail out"

In acute coronary dissection, intracoronary stents seem to stabilise the dissected arterial segment, preventing occlusion of the lumen by intimal flaps and possibly reducing the propensity to thrombosis by holding intimal flaps over exposed subintima.[16] Four studies have suggested that the need for emergency coronary bypass surgery is reduced when stents are used to treat acute occlusion of the coronary artery.[17–20] There are few data, however, on the long-term follow up of patients "salvaged" in this way.[9,20] Preliminary results from Fajadet *et al*[20] show a 33% restenosis rate nine months after emergency stenting for "bail out" of unstable lesions.

Definite conclusions about the value of stents for "bail out" are difficult because of the lack of long-term data and because in many cases stents cannot be used because of the difficulties with delivery into tortuous arteries or to distal sites. Other bail out strategies such as perfusion catheters may be equally successful[21] and randomised comparison of stents with these other methods are needed to assess their proper role in the treatment of acute occlusion.

Stents to reduce secondary restenosis

It may be useful to distinguish restenosis occurring in patients who have not previously undergone angioplasty at that site, which may be termed "primary restenosis", from restenosis occurring at a site that has already restenosed after a previous angioplasty (secondary restenosis). It was hoped that intracoronary stents would reduce the rate of restenosis in lesions that had previously restenosed,[22] and initial results were encouraging.[23,24] Subsequent experience with stents at the site of previous restenosis[8,25,26] showed restenosis rates approaching those after conventional balloon angioplasty in this situation.[27] When multiple stents have been placed in one coronary artery both restenosis[5,28,29] and thrombotic occlusion[7] are particularly common.

Stents to reduce primary restenosis

The results of coronary stenting de novo—that is as part of the initial procedure—are more promising, with restenosis rates of between 7% and 18%.[9,28–30] However, the routine use of stents for all lesions would considerably increase the cost and complexity of coronary angioplasty. It would therefore be logical to use stenting at the first intervention for lesions with an especially high risk of restenosis, such as lesions in the proximal left anterior descending coronary artery.[31] Restenosis is also common after angioplasty of coronary vein grafts,[32,33] and early results suggest that stenting might be appropriate as the initial treatment in this situation.[34]

Stent to reduce distal embolisation

Another complication of balloon angioplasty to bulky vein graft lesions is distal embolisation of plaque debris in 2–3% of cases.[32,33] Placement of an intracoronary stent simultaneously with the first dilatation might trap such material and reduce this problem: in one series of 57 stent placements in vein grafts there were no episodes of distal embolisation (Dr U Sigwart, personal communication) but as yet there is no definitive data on this point.

High success rates in stent placement

The rate of successful implantation of stents was 98% reported by Haude and colleagues[5] and rates of 94%–100% have been reported by other groups.[6,7,9,20,33] However, these success rates apply to patients who may have been selected on the basis of their suitability for stenting, excluding those with small or tortuous vessels or both, and therefore may not apply to the general population of patients undergoing coronary angioplasty. In most cases predilatation with a conventional balloon may be necessary before a stent can be introduced into the lesion.[5] Lower profile and more flexible designs of stent should increase the number of patients who can be treated by this technology.

Thrombosis and haemorrhage

In studies using early designs of stents thrombotic occlusion was frequent and the vigorous anticoagulant and antiplatelet treatment intended to prevent this in turn caused haemorrhagic complications. In the study of Haude *et al*[5] using the Palmaz-Schatz stent patients received heparin and dextran infusions during the procedure, and thereafter aspirin, dipyridamole, and coumarin. Acute or subacute thrombosis of the stent occurred in eight of their 50 patients and bleeding complications in nine. Schatz, Palmaz, and colleagues reported subacute thrombosis of their stent in 15% of 39 patients in whom stenting was followed by aspirin and dipyridamole, and in only 0·6% of 174 patients given aspirin, dipyridamole, and warfarin.[7] However, almost 10% of the 174 had serious haemorrhagic complications including two cases of tamponade, one of intracranial haemorrhage, four of gastrointestinal bleeds requiring transfusion, eight haematomas requiring surgery or transfusion or both, and two femoral pseudoaneurysms. Current data suggest that carefully controlled anticoagulant regimens are able to prevent stent thrombosis and are associated with lower rates of haemorrhagic complications.[35]

Careful selection of lesions suitable for stenting may also reduce the risk of thrombosis and the need for vigorous anticoagulation. It is now appreciated that the risk of thrombosis depends on stent diameter: thrombosis occurred in 16% of patients with smaller diameter stents (expanded to 3·5 (0·5) mm) and only 3% of those with larger stents (expanded to 4·1 (0·8) mm).[36] Thrombosis was also more common when multiple stents were placed in an artery,[6 7 36] although multiple stents in different coronary arteries do not seem to cause additional problems. Current recommendations are that stents are placed only in vessels that are expected to attain a diameter of >3 mm after dilatation and that as few stents as possible are placed in any one coronary artery.

Stent materials and design

There has been much discussion concerning the materials and designs of stents. Inadvertent deployment may be a problem of self-expanding stents; balloon rupture sometimes occurs during deployment of balloon expanded stents. Most coronary stents are difficult to visualise in patients because of the small mass of radio-opaque material. This causes difficulties with accurate placement within the lesion, and may lead to confusion if the operator suspects that the stent has become detached and embolised; radio-opaque markers have now been added to some stent delivery systems. Increased axial flexibility of stents would improve the ability to deliver them in tortuous coronary arteries and might reduce the risk of damage to the arterial wall.[37] Placement of stents distally or in tortuous arteries may also be aided by soft-tipped 5 French flexible sheaths (Teleguide (Schneider) and SDS (Johnson & Johnson)). The balloon and stent can be advanced into the coronary lesion within the sheath, over an angioplasty guide wire. The sheath is then withdrawn, leaving the stent and balloon within the lesion. This technique reduces the risks of inadvertent stent displacement and of coronary dissection during passage of the stent through the proximal coronary artery.

The material of the stent influences the mechanical properties and also the propensity to thrombosis and to endothelialisation. Positively charged metal such as stainless steel are thrombogenic unless highly polished[38]; negatively charged metals are less thrombogenic but most are corrosive.[39] Biodegradable materials may provide short term support of the arterial segment without long term risks of thrombosis,[40 41] but such stents are not yet available for clinical trials. Other possibilities include eluting stents that slowly release drugs to reduce thrombosis and restenosis,[42] coated stents with surface-bonded anticoagulant factors,[43] and seeded stents coated with cultured endothelial cells.[44 45]

Unfortunately the cost of intracoronary stents may well limit their use; the only coronary stent currently available costs approximately £500, excluding the cost of the balloon. Formal cost-benefit analyses are needed that include comparison with standard balloon angioplasty, with other devices, and with coronary bypass surgery.

Opinion

At present, the use of intracoronary stents in the United Kingdom is limited to a few centres. In our opinion, stents should be available in all centres for bail out procedures for acute dissections which cause or threaten acute coronary occlusion and perhaps for other selected cases such as vein graft angioplasty. Recent clinical experience suggests that, with the Palmaz-Schatz stent at least, the acute risk of thrombosis can be controlled to an acceptable level without unacceptable risks of haemorrhage. Medium-term anticoagulant and long-term antiplatelet therapy are important to minimise thrombosis, and close follow up of patients is essential.

It seems likely that stents will prove useful adjuncts to conventional angioplasty: experience to date is not yet sufficient to formulate guidelines for clinical use. Multicentre studies of primary coronary stenting to reduce primary restenosis are in progress. Mechanical factors alone are unlikely to prevent restenosis—perhaps a combination of the mechanical advantages of stents with pharmacological intervention will solve this problem.

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1 Waller BF. "Crackers, breakers, stretchers, drillers, scrapers, shavers, burners, welders and melters"—the future treatment of atherosclerotic coronary artery disease? A clinical-morphological assessment. *J Am Coll Cardiol* 1989;13:969–87.
2 Sigwart U. Percutaneous transluminal coronary angioplasty: what next? *Br Heart J* 1990;63:321–2.
3 King SB III. Vascular stents and atherosclerosis. *Circulation* 1989;79:460–2.
4 Serruys PW, Beatt KJ, van der Giessen WJ. Stenting of coronary arteries. Are we the sorcerer's apprentice? *Eur Heart J* 1989;10:774–82.
5 Haude M, Erbel R, Straub U, Dietz U, Meyer J. Short and long term results after intracoronary stenting in human coronary arteries: monocentre experience with the balloon-expandable Palmaz-Schatz stent. *Br Heart J* 1991;66:337–45.
6 Levine MJ, Leonard BM, Burke JA, *et al*. Clinical and angiographic results of balloon-expandable intracoronary stents in right coronary artery stenosis. *J Am Coll Cardiol* 1990;16:332–9.
7 Schatz RA, Baim DS, Leon M, *et al*. Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation* 1991;83:148–61.
8 Serruys PW, Strauss BH, Beatt KJ, *et al*. Angiographic follow-up after placement of a self-expanding coronary artery stent. *N Engl J Med* 1991; 324:13–7.
9 Goy JJ, Sigwart U, Vogt P, *et al*. Long-term follow-up of the first 56 patients treated with intracoronary self-expanding stents (the Lausanne experience). *Am J Cardiol* 1991;67:569–72.
10 Gruentzig AR, King SB, Schlumpf M, Siegenthaler W. Long-term follow-up after percutaneous transluminal coronary angioplasty: the early Zurich experience. *N Engl J Med* 1987;316:1127–32.
11 Serruys PW, Luitjen HE, Beatt KJ, *et al*. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 patients at 1, 2, 3 and 4 months. *Circulation* 1988;77:361–71.
12 Nobuyushi M, Kimura T, Nosaka H, *et al*. Restonosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol* 1988;12:616–23.
13 Ellis SG, Roubin GS, King SB III, *et al*. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988;77:372–9.
14 Detre KM, Holmes DR, Holubkov R, *et al*. Incidence and consequences of periprocedural occlusion: the 1985–1986 National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry. *Circulation* 1990;82:739–50.
15 Schatz RA. A view of vascular stents. *Circulation* 1989;79:445–57.
16 Fischman DL, Savage MP, Leon MB, *et al*. Effect of intracoronary stenting on intimal dissection following balloon angioplasty: results of qualitative and quantitative coronary analysis [abstract]. *J Am Coll Cardiol* 1990;15 (suppl):119.
17 Sigwart U, Urban P, Golf S, *et al*. Emergency stenting for acute occlusion after coronary balloon angioplasty. *Circulation* 1988;88:1121–7.
18 Roubin GS, Douglas JS, Lembo NJ, *et al*. Intracoronary stenting for acute

closure following percutaneous transluminal coronary angioplasty (PTCA) [abstract]. *Circulation* 1988;78(suppl II):407.
19 de Feyter PJ, DeScheerder I, van den Brand M, Laarman G, Suryapranata H, Serruys PW. Emergency stenting for refractory acute coronary artery occlusion during coronary angioplasty. *Am J Cardiol* 1990;66:1147–50.
20 Fajadet JC, Marco J, Cassagneau BG, Robert GP. Emergency coronary stenting for acute dissection during PTCA [abstract]. *J Am Coll Cardiol* 1991;17(suppl):53.
21 Hinohara T, Simpson JB, Phillips HR, *et al.* Transluminal catheter reperfusion: a new technique to re-establish blood flow after coronary occlusion during percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1986;57:684–6.
22 Block PC. Restenosis after percutaneous transluminal coronary angioplasty: anatomic and pathophysiological mechanisms. *Circulation* 1990;81(suppl IV):2–4.
23 Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenbarger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316:701–6.
24 Sigwart U, Kaufman U, Goy J-J, *et al.* Prevention of coronary restenosis by stenting. *Eur Heart J* 1988;9(suppl C):31–7.
25 Urban P, Sigwart U, Kaufman U, Kappenberger L. Restenosis within coronary stents: possible effect of previous angioplasty [abstract]. *J Am Coll Cardiol* 1989;13(suppl):107.
26 Ellis SG, Savage M, Baim D, *et al.* Intracoronary stenting to prevent restenosis: preliminary results of a multicenter study using the Palmaz-Schatz stent suggest benefit in selected high-risk patients [abstract]. *J Am Coll Cardiol* 1990;15(suppl):118.
27 Quigley PJ, Hlatky MA, Hinohara T, *et al.* Repeat percutaneous transluminal coronary angioplasty and predictors of recurrent restenosis. *Am J Cardiol* 1989;63:409–13.
28 Teirstein PS, Cleman MW, Hirshfeld JW, Buchbinder M, Walker C. Influence of prior restenosis on subsequent restenosis after coronary stenting [abstract]. *Circulation* 1990;82(suppl III):657.
29 Fajadet JC, Marco J, Cassagneau BG, *et al.* Restenosis following successful Palmaz-Schatz intracoronary stent implantation [abstract]. *J Am Coll Cardiol* 1991;17(suppl):346.
30 Puel J, Rousseau H, Joffre F, *et al.* Intravascular stents to prevent restenosis after transluminal coronary angioplasty [abstract]. *Circulation* 1987;76 (suppl IV):27.
31 Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS Jr, King SB III. Restenosis after successful coronary angioplasty in patients with single vessel disease. *Circulation* 1986;73:710–7.
32 Cote G, Myler RK, Stertzer SH, *et al.* Percutaneous transluminal coronary angioplasty of stenotic coronary artery grafts: 5 years' experience. *J Am Coll Cardiol* 1987;9:8–17.
33 Dorros G, Lewin RF, Mathiak LM, *et al.* Percutaneous transluminal coronary angioplasty in patients with two or more previous coronary artery bypass grafting operations. *Am J Cardiol* 1988;61:1243–7.
34 Urban P, Sigwart U, Golf S, *et al.* Intravascular stenting for stenosis of aortocoronary venous bypass grafts. *J Am Coll Cardiol* 1989;13:1085–91.
35 Schatz RA, Leon M, Baim D, *et al.* Short-term clinical results and complications with the Palmaz-Schatz coronary stent [abstract]. *J Am Coll Cardiol* 1990;15(suppl):117.
36 Sigwart U, Urban P, Sadeghi H, Kappenberger L. Implantation of 100 coronary artery stents: learning curve for the incidence of acute early complications [abstract]. *J Am Coll Cardiol* 1989;13(suppl):107.
37 Duprat G, Wright KC, Charnsangavej C, Wallace S, Gianturco C. Self-expanding metallic stents for small vessels: an experimental evaluation. *Radiology* 1987;162:469–72.
38 Baier RE, Dutton RC. Initial events in interactions of blood with a foreign surface. *J Biomed Mater Res* 1969;3:191–206.
39 De Palma VA, Baier RE, Ford JW, Glott JW, Furuse A. Investigation of three surface properties of several metals and their relation to blood compatibility. *J Biomed Mater Res* 1972;6:37–75.
40 Slepian MJ, Schindler A. Polymeric endoluminal paving/sealing: a biodegradable alternative to intracoronary stenting. *Circulation* 1988;78 (suppl IV):409.
41 Zhang C. Dissolvable supporting in small artery anastomosis: an experimental study. (Chinese with English abstract.). *Chung-Hua Wai Ko Tsa Chih* 1990;28:470–72.
42 Slepian MJ. Polymeric endoluminal paving and sealing: therapeutics at the crossroad of biochmechanics and pharmacology. In: Topol EJ, ed. *Textbool of Interventional Cardiology*. Philadelphia: W B Saunders, 1990: 665–7.
43 Bonan R, Bhat K, Lefevre T, Lemarbre L, Palement P, Wolff R, Leung TK. Coronary artery stenting after angioplasty with self-expanding parallel wire metal stents. *Am Heart J* 1991;121:1522–30.
44 Wilson JM, Brinyi LK, Salomon RN, *et al.* Implantation of vascular grafts lined with genetically modified endothelial cells. *Science* 1989;244:1344–6.
45 Dichek DA, Neville RF, Zweibel JA, Freeman SM, Leon MB, Anderson F. Seeding of intravascular stents with genetically engineered endothelial cells. *Circulation* 1989;80:1347–53.

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Editorial

Diagnostic techniques in suspected thoracic aortic dissection

Although mortality in thoracic aortic dissection remains high, early accurate diagnosis, particularly in patients with a type A dissection, can lead to life-saving surgical intervention. Several imaging techniques can now establish the diagnosis. The availability and usefulness of these techniques vary with different centres.

Transthoracic echocardiography

After presenting at a district general hospital the patient with a suspected dissection should undergo transthoracic echocardiography. Most district hospitals now have either a technician or a cardiologist capable of performing a thorough echocardiographic examination. The advantages of echocardiography are the speed and relative ease with which the technique can be used in a haemodynamically compromised patient. Reports of the accuracy of the method vary. The key echocardiographic sign is the detection of a flap of intima and media within the lumen of the aorta. Different studies have shown a sensitivity of between 14% and 100%.[1–3] Other findings such as aortic root dilatation, thickening of the aortic wall, and evidence of a pericardial effusion or aortic regurgitation are nonspecific. The studies indicated that transthoracic echocardiography is limited in its usefulness[1–3]; though if skilled operators are available, it certainly has a role in triage at the district general hospital.

Computed tomography

Computed tomography has had a considerable impact on the management of patients with suspected dissection, both in the district general hospital and in the tertiary referral centre. The detection of a flap establishes the diagnosis and the anatomical extent of the dissection can be determined. Good quality, high density images that do not show a flap imply that dissection is extremely unlikely. However, poor quality images with inadequate opacification and movement and streak artefact are not uncommon and cannot securely exclude a diagnosis of dissection.[4] In addition, computed tomography gives no information on left ventricular function or aortic regurgitation—both important determinants of survival. In addition the images require interpretation by an experienced radiologist. Patients with a negative or inadequate CT scan in whom there is continuing doubt over the clinical diagnosis should undergo coronary and aortic angiography.[5]

Transoesophageal echocardiography

Upon transfer to the referral centre the patient and any available investigations should be reviewed by a cardiologist, a cardiothoracic surgeon, and a radiologist. If all are satisfied with the diagnosis and information provided, the appropriate course of management can be started. If not, other diagnostic techniques should be used. Transoesophageal echocardiography is becoming increasingly popular because unlike transthoracic echocardiography, it is not affected by the structure of the thoracic cage or by respiratory movements. It provides high quality images of both the ascending and descending aorta, although the trachea may obscure part of the ascending aorta and arch.[6] In several series sensitivities and specificities of up to 99% were reported: these are as good as both aortography and computed tomography.[7–9] In centres with experienced operators there is no doubt that transoesophageal echocardiography can provide rapid and accurate diagnostic information. Unless performed expeditiously and with adequate sedation, transoesophageal echocardiography can increase systolic blood pressure. The main limitation in the use of this technique is the lack of appropriately trained operators. The provision of an adequate transoesophageal echocardiography service requires not only the appropriate equipment but also at least three experienced operators. Currently few centres are in a position to provide such a service, but it is likely that as experience with the technique becomes more widespread it will be used more often in patients with suspected dissection.

Intravenous digital subtraction angiography

Intravenous digital subtraction angiography has found favour in some centres and has obvious advantages. It is quick and easy to perform and only minimally invasive. Furthermore, its sensitivity and specificity are said to approach that of aortography.[10] However, the equipment is not always available and the sensitivity and specificity are little better than with computed tomography, which is more widely available. Most surgeons would not operate solely on the basis of a digital subtraction angiogram but digital angiography may be a useful screening procedure.

Magnetic resonance imaging

A recent study suggests that magnetic resonance imaging has 100% specificity and sensitivity in diagnosing the presence of dissection compared with the reference diagnostic techniques of angiography, surgery, or necropsy.[11] Magnetic resonance imaging was better than transoesophageal echocardiography, with fewer false positive diagnoses of dissection in the ascending aorta. Transoesophageal echocardiography has the advantage of taking less time than magnetic resonance imaging, though in the population studied no complications arose from the time spent in the scanner.

Aortography

Traditionally aortography has been accepted as the reference standard against which newer diagnostic techniques should be compared. There is considerable justification for this belief. Several very large multicentre studies have been performed and have shown sensitivities between 90% and 98%.[12 13] In addition, and perhaps of even more importance, aortography has been available since 1949 and consequently both cardiologists and cardiothoracic surgeons have developed considerable confidence in it. The aortogram provides information on the presence and severity of associated aortic regurgitation and, if it is negative, it may be useful to proceed to coronary angiography to investigate alternative diagnoses. Aortography can give false negative results, however,[6 14] and of the diagnostic techniques available it carries the highest risk. In the future it is likely to be superseded by the newer imaging techniques.

Coronary angiography

Is coronary angiography necessary in patients in whom the diagnosis of dissection has been established? There is no published evidence that performing coronary angiography lowers mortality in patients with dissection.[15] Most cardiologists and cardiothoracic surgeons think that coronary angiography in the presence of a very dilated ascending aorta substantially lengthens the procedure thereby exposing the patient to extra risk. In the absence of evidence to the contrary there seems no reason to perform coronary angiography routinely in patients in whom the diagnosis of dissection has been established.

Conclusions

We believe that if a good quality, high resolution computed tomography scan shows a dissection then no other investigation is necessary. A negative high quality computed tomographic scan in the district general hospital will usually avoid an inconvenient and costly transfer to a regional centre. If, however, no scan is available, the scan is non-diagnostic, or sufficient clinical suspicion remains despite a negative scan the patient should be transferred without delay. At the referral centre, in future, transoesophageal echocardiography is likely to be performed as the next diagnostic procedure. Magnetic resonance scanning will be increasingly available and useful in this setting with angiography being used largely to investigate the coronary arteries in patients in whom doubts about the diagnosis persist.

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1 Granto DE, Dee P, Gibson RS. Utility of two-dimensional echocardiography in suspected ascending aortic dissection. *Am J Cardiol* 1985;56:123–9.
2 Smackler AR, Rosmir AM, Watts LE, Hackshaw BT. Echocardiographic diagnosis of aortic root dissection by M-mode and two-dimensional techniques. *Am Heart J* 1982;103:897–904.
3 McLeod AA, Monaghan MJ, Richardson PJ. Diagnosis of acute aortic dissection by M-mode and cross-sectional echocardiography: a five year experience. *Eur Heart J* 1983;4:196–202.
4 Vassile N, Mathieu D, Keita K, *et al.* Computed tomography of thoracic aortic dissection: accuracy and pitfalls. *J Comput Assist Tomogr* 1986; 10:211–5.
5 Morgan JM, Oldershaw PJ, Gray HH. Use of computed tomographic scanning and aortography in the diagnosis of acute dissection of the thoracic aorta. *Br Heart J* 1990;64:261–5.
6 Mugge A, Daniel WG, Laas J, Grote R, Litchtlen PR. False-negative diagnosis of proximal aortic dissection by computerised tomography or angiography and possible explanations based on transoesophageal echocardiographic findings. *Am J Cardiol* 1990;65:527–8.
7 Erbel R, Engberding R, Daniel W, Roelandt J, Visser C, Rennollet H. Echocardiography in diagnosis of aortic dissection. *Lancet* 1989;i:457–61.
8 Enia F, Ledda G, Lo Maura R, Matassa C, Raspanti G, Stabile A. Utility of echocardiography in the diagnosis of aortic dissection involving the ascending aorta. *Chest* 1989;95:125–9.
9 Godwin JD, Herfkens RL, Skioldebrand CG, Ferdele MP, Lipton MJ. Evaluation of dissections and aneurysms of the thoracic aorta by conventional and dynamic CT scanning. *Radiology* 1980;136:125–33.
10 Lyons JL, Gershlick A, Gardener J, Layton C. Arrival time analysis of intravenous digital aortograms in aortic dissection. *Br Heart J* 1988; 166:651–5.
11 Nienaber CA, Spielmann RP, von Kodolitsch Y, *et al.* Diagnosis of thoracic aortic dissection: magnetic resonance imaging versus transesophageal echocardiography. *Circulation* 1992;85:434–48.
12 Slater EE, De Sanctis RW. The clinical recognition of dissecting aortic aneurysm. *Am J Med* 1976;60:625–33.
13 Smith DC, Jang CC. Radiological diagnosis of aortic dissection. In: Doroghazi RM, Slater EE, eds. *Aortic dissection*. New York: McGraw-Hill, 1983:71–132.
14 Shuford WH, Sybers RG, Weens HS. Problems in aortographic diagnosis of dissecting aneurysm of the aorta. *N Engl J Med* 1969;280:225–31.
15 Kern MJ, Serota H, Callicoat P, *et al.* Use of coronary arteriography in the preoperative management of patients undergoing urgent repair of the thoracic aorta. *Am Heart J* 1990;119:143–8.

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REVIEW

Exercise training as therapy for chronic heart failure

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Patients with impaired left ventricular function have a reduced exercise capacity because of dyspnoea and fatigue; and exercise testing has become an integral part of the assessment of patients with chronic heart failure in many cardiac centres.[1] Over the past decade, several groups have shown that there is also a clinical benefit from using regular exercise testing and training as adjunctive therapy in the treatment of selected patients with chronic heart failure. The underlying mechanisms responsible for the beneficial effect of exercise training are now becoming apparent.

Normal cardiovascular response to exercise

During isotonic exercise the contraction of skeletal muscle in movement provides a volume rather than a pressure load to the left ventricle, and the cardiovascular response is proportional to the severity of the exercise.[2] The human body responds to dynamic exercise so that the blood flow to exercising muscles is increased to maintain oxygen delivery, heat is dissipated, and flow to vital organs such as the brain and heart is preserved. The cardiac output, the oxygen capacity of the blood (dependent on arterial oxygen saturation and haemoglobin concentration), and the vascular bed of exercising and non-exercising skeletal muscle all function concordantly to ensure that oxygen delivery approximates to oxygen demand. The intensity of exercise may be quantified by the maximal oxygen consumption (the product of maximum cardiac output and maximum arteriovenous oxygen ($a - v\ O_2$) difference) which is the greatest amount of oxygen an individual can use during dynamic exercise to deliver to skeletal muscle.[3] Because the $a - v\ O_2$ difference has a physiological limit, at true maximal effort maximal oxygen consumption is an estimate of maximal cardiac output.[2]

The normal response to exercise is an increase in cardiac output with an overall reduction in systemic vascular resistance caused by vasodilatation in exercising muscle and a subsequent small increase in arterial blood pressure.[4] Other peripheral adaptations include the central displacement of venous blood through muscle contraction of the exercising limbs and the abdominal and thoracic muscles. The cardiac response to exercise occurs through the integrated effects of tachycardia, increased adrenergic stimulation, and the Frank-Starling mechanism.[4] In mild to moderate exercise the heart rate parallels increasing cardiac output mainly through loss of vagal restraint. With more strenous exercise adrenergic activation supplements this exercise tachycardia and increases myocardial contractility, leading to an increased stroke volume (with an increase in end diastolic volume through the Frank-Starling mechanism). Other adaptations improving peripheral oxygen delivery are an increased oxygen extraction in exercising muscles and the rightward shift of the oxygen-haemoglobin dissociation curve.[4] With regular training, healthy people may develop a lower heart rate at rest and on exercise. In trained athletes additional ventricular hypertrophy and dilatation facilitate a higher and more sustained cardiac output on exercise.

Cardiovascular response to exercise in chronic heart failure

In the early stages of chronic heart failure compensatory mechanisms maintain cardiac output. These are an increase in end-diastolic volume with increased preload (the Frank-Starling mechanism), left ventricular hypertrophy, and the increased neurohormonal response. As heart failure progresses, however, an inability to increase adequately cardiac output in response to exercise develops, with an additional decrease in skeletal muscle perfusion at rest and on exercise associated with an increased vascular resistance in exercising muscle.[5] Although cardiac output can be redistributed through vasoconstriction so that blood flow to exercising muscles and vital organs is conserved, this compensatory response may become defective. As a consequence arterial blood pressure is maintained on exercise to preserve flow to non-exercising vascular beds to the detriment of blood flow to exercising muscle at rest and on exercise.[5] Maximal oxygen extraction in exercising muscle is reached more quickly than in healthy individuals and there is greater reliance on anaerobic metabolism. The reduction in blood flow to the exercising skeletal muscle, and thus in oxygen delivery, relates closely to the reduced peak cardiac output and exercise capacity in these patients.[5–7]

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References: 1. Chung M *et al. Hosp Formul* 1990; **25** (Suppl A): 15-19. **2.** Cruickshank J M & McCainsh J. *Acta Therapeutica* 1992; **18:** 53-59. **3.** Data on file.

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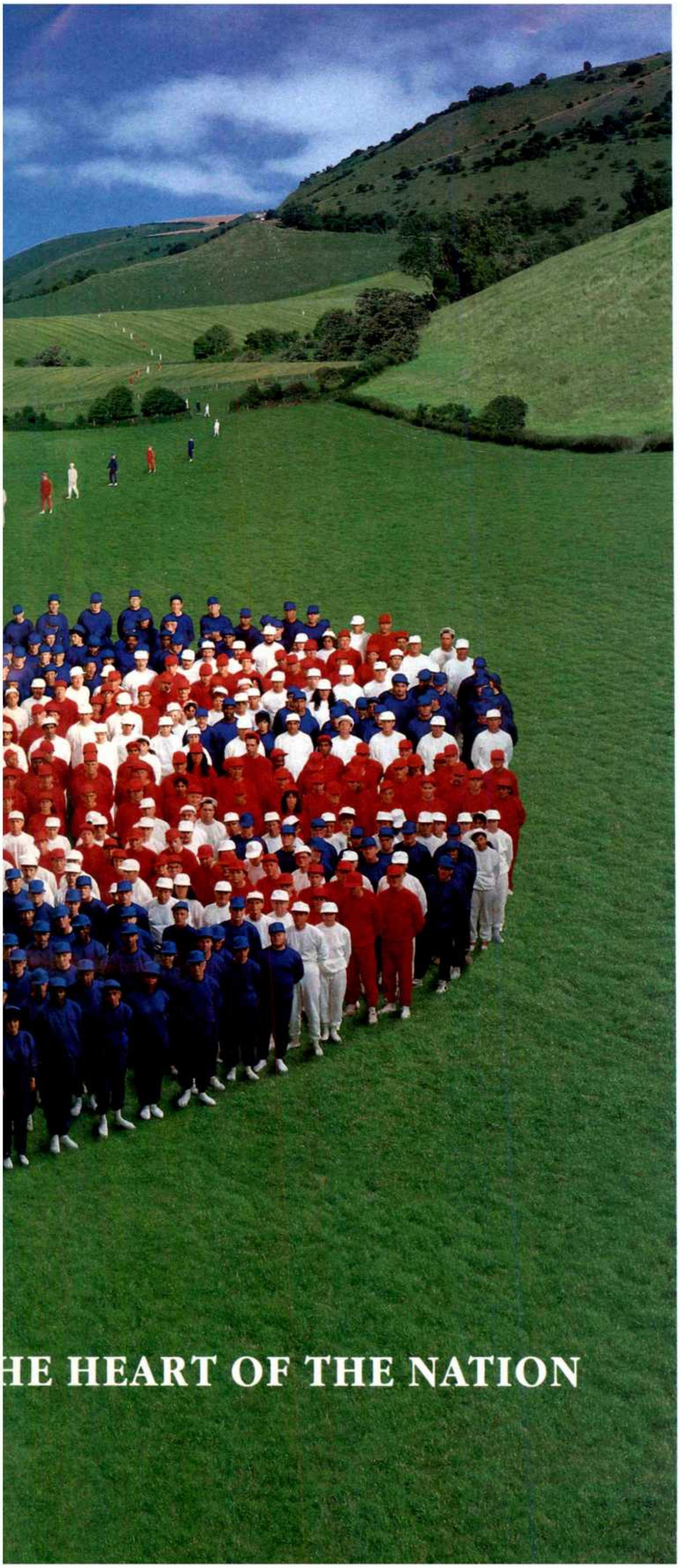
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REFERENCES
1. OPCS Monitor DH2. June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.,* 1984, **251,** 351.

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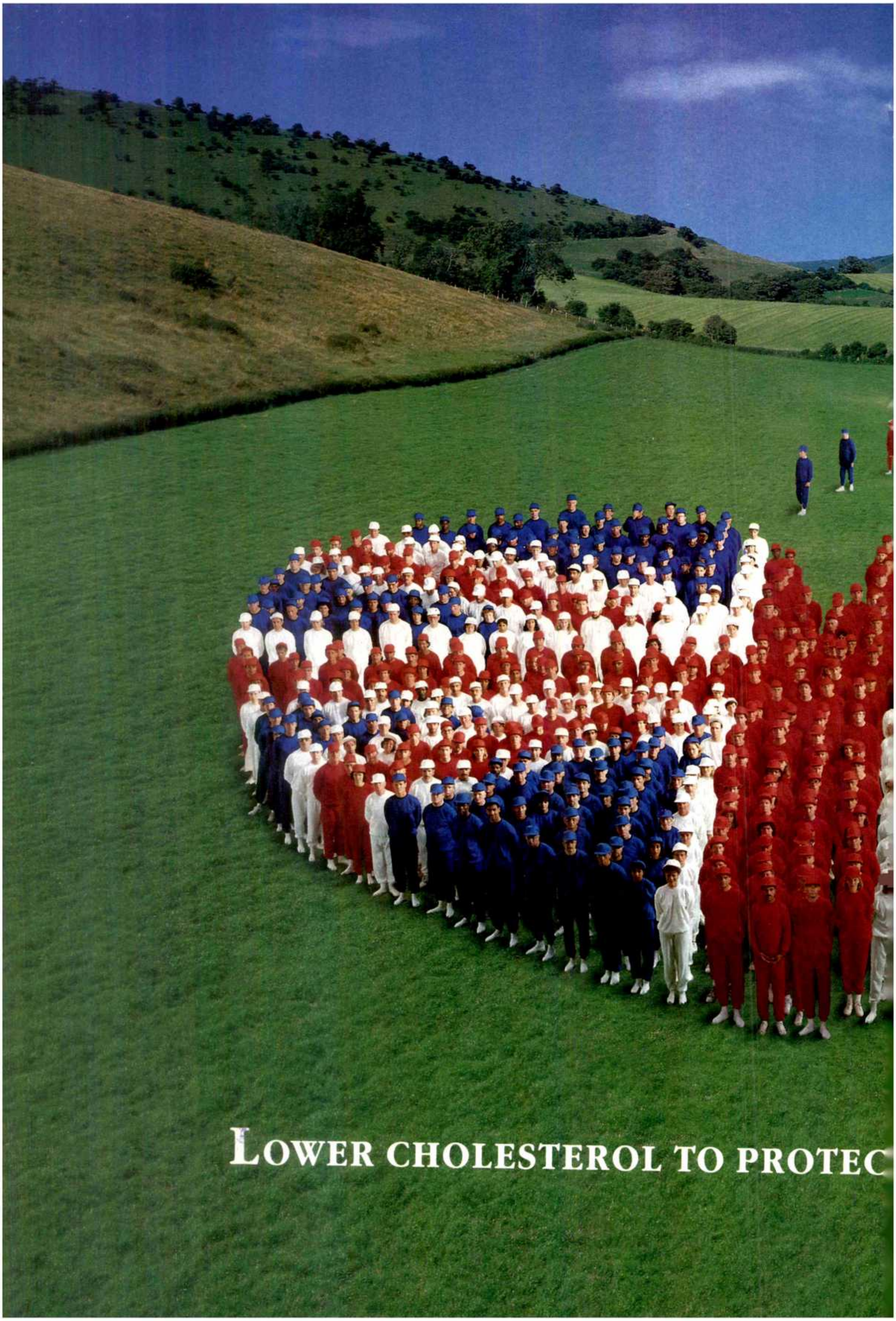
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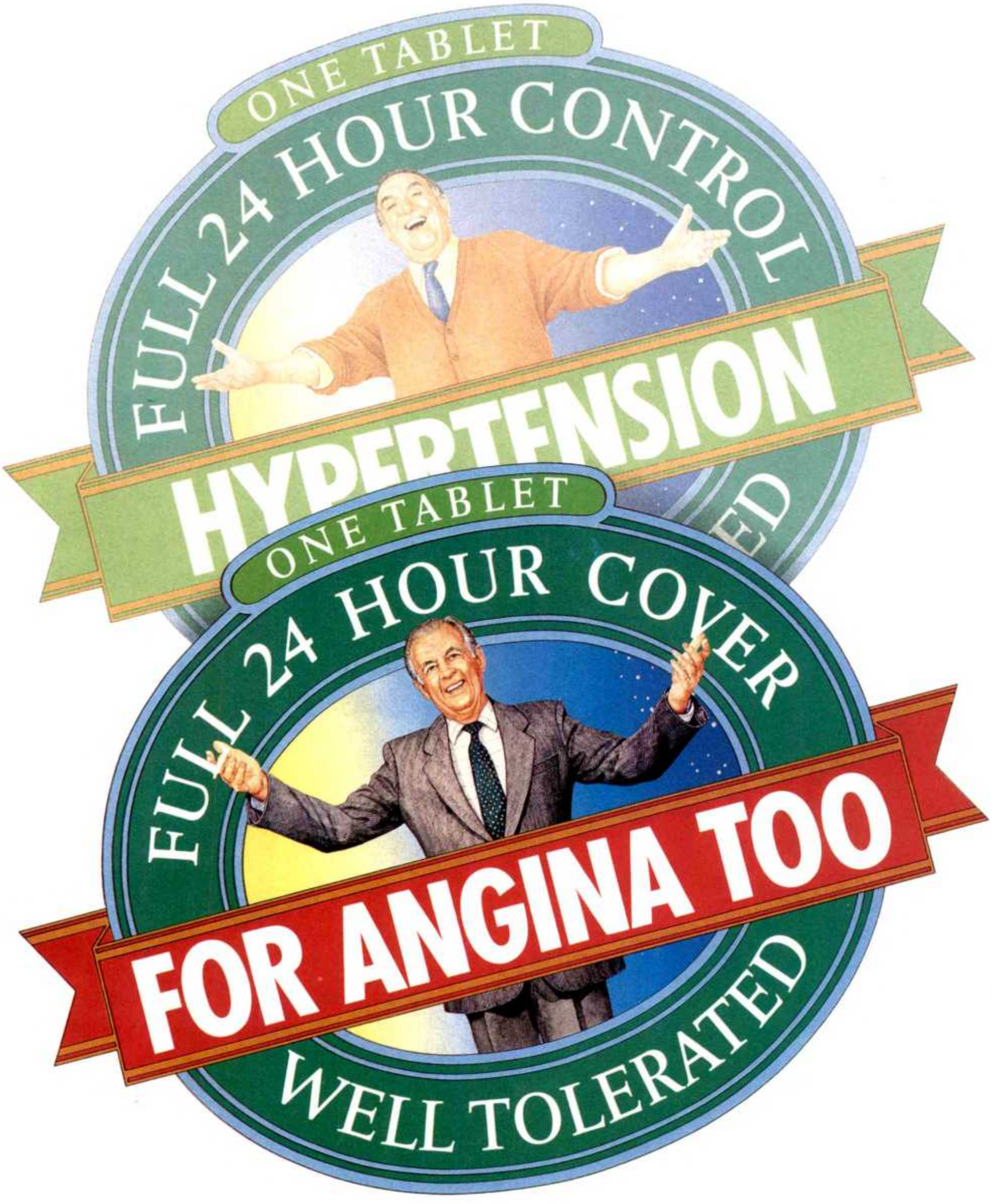

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ditioning, the vasoreactivity of the skeletal muscle vascular bed becomes impaired and the oxidative capacity is altered. Several histological and histochemical changes have been noted in the skeletal muscle of patients with heart failure. In different studies, atrophy of type I fibres[8-10] and type II fibres[8 11 12] or an increased percentage of type IIb fibres[10 12] have been reported. These resemble the changes seen after deconditioning in healthy people.

A reduction in blood flow to exercising limbs during submaximal and maximal exertion was an early peripheral abnormality found in chronic heart failure.[13] Further work showed that this failure to augment maximal blood flow adequately in exercising muscle may occur independently of cardiac performance on exercise.[14] Maximal blood flow to exercising skeletal muscle is reduced in chronic heart failure to some extent as a result of a normal mean arterial blood pressure being maintained.[5] This reduced flow results from a reduced muscle driving pressure (arterial minus venous pressure) as well as impaired vasodilatation in the muscle bed.[13 14] However, at a given work rate, forearm muscle blood flow was similar in patients with heart failure and in healthy controls,[15] implying that blood flow matches workload in a small muscle group but that this linear relation does not hold in larger muscle groups where vasodilatation is impaired.

Magnetic resonance spectroscopy of high energy phosphate metabolism (^{31}P-MRS) showed excessive dependence on anaerobic glycolysis with rapid depletion of phosphocreatine and early lactic acid production in the forearm muscles of patients with chronic heart failure compared with healthy controls.[16-18] This excessive depletion of phosphocreatine on exercise occurs to a greater extent in exercising leg muscles in the absence of any difference in leg blood flow at the same workload.[15] Although Massie *et al* found a correlation between such skeletal muscle metabolic abnormalities in the forearm on exercise and the clinical severity of chronic heart failure, the skeletal muscle abnormalities were unrelated to muscle blood flow.[16] Thus the reduced exercise capacity of chronic heart failure cannot be explained by changes in muscle blood flow alone.

It is likely that there is a defect of oxidative metabolism in skeletal muscle in chronic heart failure, which is consistent with the reduction in volume of mitochondrial cristae in skeletal muscle cells.[19] Although concentrations of glycolytic enzymes are reported to be normal,[10 12] mitochondrial enzymes involved in substrate use such as succinate dehydrogenase and β-hydroxyacyl-coenzyme A dehydrogenase are reduced.[10] However, it has been difficult to correlate early phosphocreatine depletion with such histochemical abnormalities.[12]

Exercise training as therapy

Formerly, exercise training in patients with chronic heart failure was believed to be harmful, causing worsening of symptoms and further compromising cardiac function. Though there is some evidence to suggest that exercise training may cause further changes in left ventricular wall thinning and shape distortion in patients with a large degree of ventricular asynergy soon after myocardial infarction,[20] there is no evidence for functional deterioration in patients with well compensated chronic heart failure.[21] Several studies over the past decade showed that exercise programmes were not harmful but were of benefit when carefully controlled protocols were used.[22-25] Exercise capacity measured as maximal oxygen consumption or exercise duration may be increased and this increase is associated with several beneficial peripheral and metabolic adaptations.[22-25] The remaining uncertainties about exercise as a treatment relate to patient selection and to the optimal intensity and duration of therapy.

Lee *et al* first showed improvement in mean exercise duration after long-term physical training in 18 patients with chronic heart failure who showed no change in resting cardiac output or central haemodynamic variables.[22] In another study to investigate the central and peripheral haemodynamic and metabolic adaptations to long-term exercise, Sullivan *et al* studied 12 patients (mean (SEM) left ventricular ejection fraction of 24 (10)%) before and four to six months after four hours of regulated exercise per week and showed a mean increase of 23% in maximal oxygen consumption.[23] There was also a reduction in heart rate at rest and submaximal exercise and an increase in the systemic $a - v\,O_2$ difference at rest and peak exercise, which was first noted after 75 days of training. There were no changes at either rest or exercise in arterial pressure, pulmonary wedge pressure, stroke volume, or ejection fraction, with only a trend towards an increase in cardiac output. The increase in the systemic $a - v\,O_2$ difference was attributed to a redistribution of cardiac output to working skeletal muscles. In addition to this central adaptation there were increases in leg blood flow (with reductions in vascular resistance) and delivery of oxygen to the leg at peak exercise, in $a - v\,O_2$ difference (greater oxygen extraction) and a reduction in lactate production at submaximal exercise. The fall in lactate production was independent of leg blood flow, implying a true peripheral adaptation independent of haemodynamic changes. There was also a significant increase in haemoglobin concentration after training. The response to exercise was unrelated to any resting variable: the change in maximal oxygen consumption correlated with the increase in cardiac output and leg blood flow and also with the amount of time spent exercising each week.[23] In another study of patients in New York Heart Association class I who followed a more intensive training regimen, Ehsani showed increases both in stroke volume and in maximal peripheral oxygen extraction.[24]

It has been suggested that some of the secondary changes seen in chronic heart failure—such as neurohormonal activation and changes in skeletal muscle and peripheral vasculature—may be a result of physical deconditioning itself. The autonomic imbalance (increased sympathetic activity) seen in moderate to severe chronic heart failure may reduce heart rate variability and thus predispose the patient to sudden death.[25] In one study, 11 patients with stable moderate to severe heart failure (left ventricular ejection fraction 19 (8)%) performed 20 minutes of daily bicycle exercise (five days a week) to 60–80% maximum heart rate over eight weeks in a crossover study with eight weeks rest. Exercise duration and maximal oxygen consumption increased by around 20%. This increase in maximal oxygen consumption correlated closely with a reduced heart rate at rest and submaximal exercise, an increased heart rate variability, and a reduced resting noradrenaline spillover, suggesting an association between the improvement in exercise capacity and reduced autonomic imbalance.[25]

Mechanisms for improvement in exercise capacity with training

The mechanism whereby the low output state of chronic heart failure alters the oxidative capacity of skeletal muscle is not known. Possible mechanisms include increased activity of the sympathetic nervous system or neurohormonal changes or chronic low grade ischaemia. The metabolic changes found in the finger flexor muscles of patients in heart failure do not support disuse as a cause in its own right.[16] Musch *et al* studied the effects of low and high intensity exercise training in rats with chronic heart failure.[26] High intensity training conferred an additional increase in the maximal $a - v\ O_2$ difference, a reduction in resting and maximal heart rate (reversal of "chronotropic incompetence") and an increase in cardiac output compared with low intensity training. Whether the extent of exercise performed in humans determines the extent of changes in skeletal muscle blood flow and metabolism is not known. Other possible adaptations accounting for the training-induced delay in anaerobic metabolism, in addition to vascular and biochemical adaptations in skeletal muscle, are a decreased adrenergic activity with exercise,[25] changes in substrate delivery, or alterations in intramuscular blood flow distribution.[15] The increase in haemoglobin concentration (which could account for increased peripheral oxygen delivery) probably occurs after training because diuretic treatment prevents an increase of plasma volume.[23]

Peripheral deconditioning accounts for the impairment of vasodilator capacity to a large degree. Sinoway *et al* showed that a unilateral programme of dynamic handgrip over 30 days led to a greater peak blood flow response to ischaemia and lower minimal vascular resistance in the trained forearm of patients with heart failure (compared with the control forearm), in the absence of changes in systemic aerobic capacity.[27] Skeletal muscle blood flow and metabolism are closely linked because the distribution of blood flow on exercise is matched to local metabolism. It is likely that the benefits of physical training also occur predominately through reversal of the reduction in oxidative capacity. In another study of the independent peripheral adaptation to regular exercise, Minotti *et al* performed a localised training regimen on the forearm of patients with heart failure. Endurance improved and was associated with a reduction in the ratio of inorganic phosphate to phosphocreatine (P_i/PCr) at ^{31}P-MRS (indirect evidence of increased oxidative capacity).[28] This occurred in the absence of changes in forearm blood flow, which implies that regulated exercise improves the metabolic response of skeletal muscle to exercise. It may be that this is a major mechanism whereby exercise training improves exercise capacity in chronic heart failure.

It is also of interest that improvement in maximal oxygen consumption may lag behind objective measurements of resting cardiac function after the start of drug treatment; this is further evidence of a coupling process between cardiac performance and circulatory and metabolic function during exercise in patients with chronic heart failure.[29]

Conclusions

Exercise training benefits patients with well-compensated chronic heart failure, even in those with considerable left ventricular impairment. It delays the onset of anaerobic metabolism in skeletal muscle reversing the impairment of peripheral vasodilatation and improving blood flow to exercising muscles. It is safe and does not induce clinical deterioration as previously believed. However, many previous studies have not taken patient motivation and thus compliance into account. More controlled studies are required to determine the intensity and duration of exercise training required. It is likely that those who show no adaptation to a low intensity training programme within six weeks should not continue with the programme.[21] The use of exercise training as a treatment in patients with chronic heart failure has provided another means of treating a pathophysiological state that otherwise has a natural history of gradual deterioration and high mortality despite early pharmacological intervention. However, whether this increase in exercise capacity can be sustained and reflected in an improved survival is not known.

1 Patterson JA, Naughton J, Pietras RJ, Gunnes RM. Treadmill exercise in the assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1972;30: 757–62.

2 Fletcher GF, Froelicher VF, Hartley H, Haskell WL, Pollock ML. Exercise standards. A statement for health professionals from the American Heart Association. *Circulation* 1990;82:2286–332.

3 Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic heart failure. *Circulation* 1982;65:1213–23.

4 Braunwald E, Ross J. Control of cardiac performance. In: Berne RM, Sperelakis N, Geiger SR, eds. *The cardiovascular system*. Vol 1: *The heart*. Baltimore: Waverly Press, 1979:550–63.

5 Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. *Circulation* 1989;80:769–81.

6 Franciosa JA, Leddy CL, Wilen M, Schwartz DE. Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. *Am J Cardiol* 1984;53:127–34.

7 Wilson JR, Martin JL, Schwartz DE, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of

impaired nutritive flow to skeletal muscle. *Circulation* 1984;69:1079–87.

8 Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol* 1988;18:187–95.

9 Caforio ALP, Rossi B, Risaliti R, Sciliano G, Marchetti A, Angelini C *et al*. Type I fiber abnormalities in skeletal muscle of patients with hypertrophic and dilated cardiomyopathy: evidence of subclinical myogenic myopathy. *J Am Coll Cardiol* 1989;14:1464–73.

10 Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation* 1990;81:518–27.

11 Dunnigan A, Staley NA, Smith SA, Pierpont ME, Judd D, Benditt DG *et al*. Cardiac and skeletal muscle abnormalities in cardiomyopathy: comparison of patients with ventricular tachycardia or congestive heart failure. *J Am Coll Cardiol* 1987;10:608–18.

12 Mancini DM, Coyle E, Coggan A. Contribution of intrinsic skeletal muscle changes to ^{31}P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation* 1989;80:1338–46.

13 Zelis R, Longhurst J, Capone RJ, Mason DT. A comparison of regional blood flow and oxygen utilisation during dynamic forearm exercise in normal subjects and patients with congestive heart failure. *Circulation* 1974;50: 137–43.

14 Lejemtel TH, Maskin CS, Lucido D, Chadwick BJ. Failure to augment maximal limb blood flow in response to one-leg versus two-leg exercise in patients with severe heart failure. *Circulation* 1986;74:245–51.

15 Arnolda L, Conway M, Dolecki M, Sharif H, Rajagopalan B, Ledingham JGG *et al*. Skeletal muscle metabolism in heart failure: a ^{31}P nuclear magnetic resonance spectroscopy study of leg muscle. *Clin Sci* 1990;79:583–9.

16 Massie BM, Conway M, Yonge R, Frostick S, Ledingham J, Sleight P *et al*. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation* 1987;76:1009–19.

17 Weiner DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation* 1986;73:1127–36.

18 Massie BM, Conway M, Rajagopalan B, Yonge R, Frostick S, Ledingham J *et al*. Skeletal muscle metabolism during exercise under ischaemic conditions in congestive heart failure. Evidence for abnormalities unrelated to blood flow. *Circulation* 1988;78:320–6.

19 Drexler H, Riede U, Schaefer H-E. Reduced oxidative capacity of skeletal muscle in patients with severe heart failure. *Circulation* 1987;76 (suppl IV):IV–178.

20 Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll Cardiol* 1988;12:362–72.

21 Kellermann JJ, Shemesh J, Ben-Ari E. Contraindications to physical training in patients with impaired ventricular function. *Eur Heart J* 1988;9 (suppl F):71–6.

22 Lee AP, Ice R, Blessey R, Sanmarco ME. Long-term effects of physical training on coronary patients with impaired LV function. *Circulation* 1979;60:1519–26.

23 Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metablic effects. *Circulation* 1988; 78:506–15.

24 Ehsani AA. Adaptations to training in patients with exercise-induced left ventricular dysfunction. *Adv Cardiol* 1986; 34:148–55.

25 Coats AJS, Adamopoulos S, Meyer T, Conway J, Sleight P. Physical training in chronic heart failure. *Lancet* 1990; 335:63–6.

26 Musch TI, Moore RL, Hilty MR. Effects of dynamic exercise training on the metabolic and cardiocirculatory responses to exercise in the rat model of myocardial infarction and heart failure. *Am J Cardiol* 1988;62: 20E–24E (Suppl).

27 Sinoway LI, Shenberger J, Wilson J, Mclaughlin D, Musch T, Zelis R. A 30-day forearm work protocol increases maximal forearm blood flow. *J Appl Physiol* 1987; 62:1063–7.

28 Minotti JR, Johnson EC, Hudson TL, Zuroske G, Murata G, Fukushima E *et al*. Skeletal muscle response to exercise training in congestive heart failure. *J Clin Invest* 1990;86:751–8.

29 Zelis R, Sinoway LI, Musch TI, Davis D, Just H. Regional blood flow in congestive heart failure: concept of compensatory mechanisms with short and long time constants. *Am J Cardiol* 1988;62:2E–8E (Suppl).

Br Heart J 1992;67:434–8

Occurrence of valvar heart disease in acute rheumatic fever without evident carditis: colour-flow Doppler identification

Gordon M Folger Jr, Rachel Hajar, Andrej Robida, Hajar Ahmed Hajar

Abstract

Objective—To determine the frequency of occurrence of mitral and aortic valvar regurgitation in rheumatic children in whom there was no evidence of carditis acutely or at an earlier attack.

Design—Colour flow Doppler imaging was used in a non-randomised study of sequentially admitted children who met the criteria for acute rheumatic fever without clinically evident carditis and patients in whom the disease was quiescent after a previous attack of rheumatic fever. Two separate control groups were used for comparison of the echocardiographic findings, and a group of patients with confirmed rheumatic carditis was included for comparison of acute phase and antistreptococcal reactants.

Setting—A general hospital with the only paediatric inpatient department in Qatar.

Patients—From November 1988 to October 1990, 11 children were studied during the acute rheumatic period. In seven additional children the disease was quiescent when they were studied 18 to 36 months after a documented episode of acute rheumatic fever in which there was no evidence of carditis. The control patients were all studied during the same period.

Main outcome measure—Detection of mitral and aortic regurgitation in patients without clinical evidence of rheumatic carditis in the acute or quiescent stages of the disease.

Results—Mitral or mitral and aortic regurgitation was found in 10 of the 11 children studied in the acute rheumatic period. None had a murmur or other evidence of carditis. In all the cases studied the valvar insufficiency was mild. Four of the children studied late in the quiescent period had either aortic or mitral insufficiency by colour flow Doppler evaluation; two children who had previously had valvar insufficiency no longer showed this, and one child without positive findings in the acute phase remained without insufficiency. None of the non-rheumatic control subjects showed mitral or aortic regurgitation.

Conclusions—Colour flow Doppler imaging is a useful method of identifing subclinical mitral and aortic valvar disease at all stages of rheumatic fever when carditis cannot be otherwise detected and is a valuable addition to current diagnostic criteria.

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It can be difficult to confirm the diagnosis of acute rheumatic fever when the only major manifestation is non-cardiac. Recurrences are common but with the patient's cooperation they can be prevented: when the heart is affected the prevention of a recurrence is vital.

We showed that Doppler echocardiography identified subclinical (that is, without auscultatory signs) degrees of valvar incompetence involving the mitral and aortic valves in children who had typical migratory polyarthritis as their only major rheumatic manifestation.[1] The purpose of this report is to extend our previous findings by the use of colour flow Doppler echocardiographic studies in both the original group of patients and in newly occurring cases.

Patients and methods

Since our preliminary report that indicated a high incidence of unsuspected mitral and aortic valve disease in a small number of acute rheumatic fever patients without evidence of carditis,[1] we have studied a consecutive series of new cases and patients from the earlier study by adding colour flow imaging to the study design. Four groups of children make up the patient population. Children in group 1 had confirmed acute rheumatic fever without clinical evidence of cardiac involvement: children evaluated since the end of the previous study made up group 1a and children from the original study were group 1b. Group 2 was made up of the new patients with obvious carditis who were compared with group 1a for indicators of acute rheumatic fever such as acute phase reactants. Group 2 was not included in the echocardiographic analysis because these children all had clinical evidence of mitral or aortic regurgitation when they entered the study. Group 3 includes children who were admitted to hospital with arthralgia or arthritis during the same period as those in group 1a and were subsequently shown not to have rheumatic fever. Patients in group 4 underwent diagnostic Doppler and colour flow echocardiography for other conditions suspected to be associated with cardiovascular problems.

The sole criterion for entrance into groups 1 to 3 of the study was suspicion by the admitting house officer of the possibility of acute rheumatic fever. In many instances this was a diagnosis by exclusion and with few exceptions was based primarily upon articular complaints and findings. A routine blood count, erythrocyte sedimentation rate, C reactive protein, antistreptolysin O titre, chest radiograph, and electrocardiogram were obtained at admission. To allow for night and weekend admissions complete cross sectional echocardiographic study including Doppler and Doppler colour flow imaging were performed within 48 hours of admission, and before any specific treatment for rheumatic fever was started.

The patients were all examined by at least two of us. At least one of us was also involved with the echocardiographic procedures. Except for group 4 patients, who were studied at random, the suspected diagnosis—rheumatic fever—was known to each of us at the time of echocardiographic study. In the initial clinical assessment and before echocardiographic evaluation, the newly presenting children in whom there was interobserver disagreement about the physical findings, principally the nature of any murmur detected, were accepted as having evidence of carditis and automatically assigned to group 2.

All studies were performed with an Accuson 128. Colour flow imaging became available to us in November 1988. This was the starting date of the current study, which finished in October 1990.

The Doppler echocardiographic guidelines used were identical to those of the previous study.[1] Briefly, regurgitant flow relative to the valve under investigation had to be holosystolic (mitral) or holodiastolic (aortic) with peak velocities for both exceeding 2·5 m/s; occasionally an envelope with terminal high velocity signals was difficult to obtain. All colour flow findings continued throughout the appropriate cardiac phase for that valve and clearly had to extend past the paravalvar region. Also, mosaic colour changes indicative of high velocity turbulence had to be seen.

Results

Every patient from the rheumatic groups (1 and 2) satisfied the major and minor aspects of the Jones criteria. Clinically the children in group 1 had only one major criterion (arthritis, chorea, or erythema marginatum) without any supportive clinical evidence of carditis; by contrast the group 2 patients all had auscultatory evidence of carditis or valvitis and thus had two major criteria. Several children from both groups had antistreptolysin O titres in the high normal range, a finding known to occur in roughly 20% of cases of acute rheumatic fever[2]; in our institution we perform no other streptococcal antibody investigations so that evidence of preceding streptococcal infection in these children was suspected but could not be confirmed.

GROUP 1A

Table 1 shows details of the 11 children in group 1a. This brings to a total of 21, including those from the preliminary study,[1] the children who make up our experience of patients with acute rheumatic fever without clinical evidence of carditis. Of these, nine presented with polyarthritis as their only major rheumatic symptom. One child had only a rash, considered to be that of erythema marginatum (patient 6). One child gave a history of chorea lasting more than one month and was having obvious choreiform movements when studied. Figures 1 and 2 show the colour flow Doppler images for this child.

No patient in group 1 showed any of the usually accepted clinical manifestations of active carditis; PR interval prolongation by itself, which was present in nearly 30% of these children, is generally considered non-specific and non diagnostic of rheumatic carditis. In addition to the absence of any murmurs even remotely suggestive of mitral or aortic regurgitation, indicators of carditis such as pericarditis, radiographic change in heart size, or tachycardia persisting longer than the febrile period were not found. Slightly less than half of these children had systolic murmurs of typically innocent quality and in the remainder no murmurs were heard. In no instance was there a history of previous rheumatic fever. All the patients, except one with chorea, were treated with aspirin as their only anti-inflammatory medication.

Table 1 Colour flow doppler imaging acute phase

Patient data						*Valvar regurgitation*					
Case	*Age sex (y)*	*Clinical diagnosis*	*ESR (mm/hr)*	*ASO*	*ECG*	*Murmur (intensity)*	*MR*	*AR*	*MR + AR*	*Follow up (months)*	*Remarks*
Group 1a (non-carditis):											
1	14, M	Arthritis	100	800	1°AVB	0	+	–	–	7	MR
2	7, M	Arthritis	96	200	N	0	+	–	–	8	Negative
3	9, M	Arthritis	100	400	1°AVB	0	+	–	–		
4	8, F	Arthritis	127	300	N	BESM (2/6)	–	–	+		
5	10, F	Arthritis	105	200	N	BESM (1/6)	–	–	+		
6	9, M	EM	125	600	N	0	–	–	–		
7	11, F	Chorea	19	300	N	0	–	–	+	6	MR + AR
8	12, M	Arthritis	99	300	1°AVB	BESM (2/6)	+	–	–		
9	9, F	Arthritis	126	1200	N	BESM (1/6)	+	–	–	3	Negative
10	10, M	Arthritis	133	400	N	0	–	–	+	1	MR + AR
11	10, F	Arthritis	118	800	N	BESM (1/6)	+	–	–		
Group 2 (carditis):											
12	7–11,		95	200	5 1°AVB	MR 4	3	–	5	Colour flow Doppler identified additional valvar involvement in 2 cases	
	M 5				3 N	AR 1					
19	F 3		130	1600		MR + AR 3					

AR, aortic regurgitation; ASO, antistreptolysin O titre; AVB, atrioventricular block; BESM, basal ejection systolic murmur; CH, chorea; EM, erythema marginatum; ESR, erythrocyte sedimentation rate; MR, mitral regurgitation; N, normal.

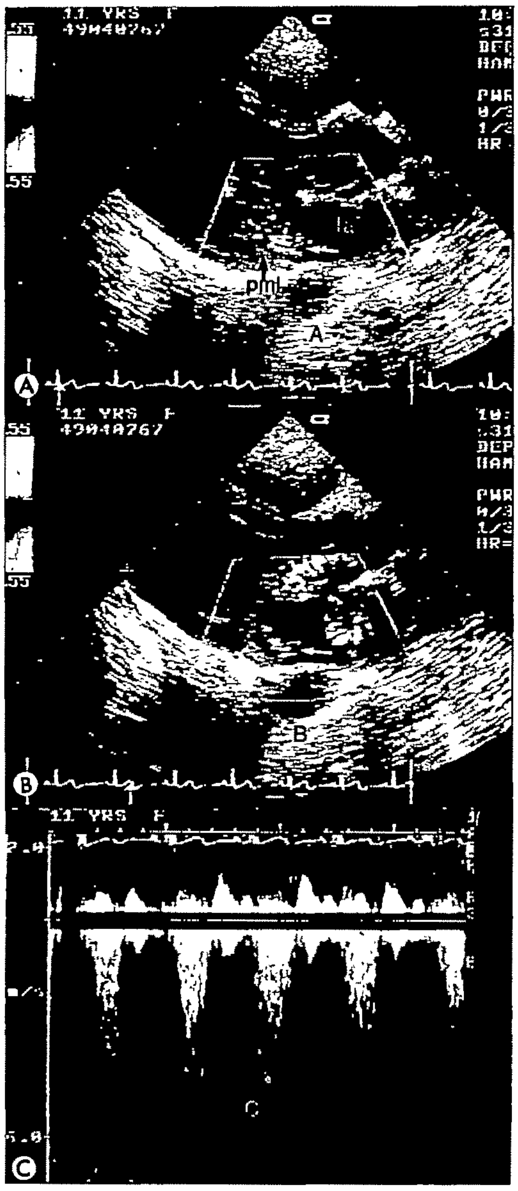

Figure 1 Colour flow Doppler imaging of mitral valve, parasternal long axis view in case 7. (A) Early systole. Note mosaic coloured flow signal (arrow) entering left atrium (la). pml, posterior mitral valve leaflet. (B) Late systole. Holosystolic incompetence identified by the persistence of the regurgitant signal. (C) Continuous wave Doppler echocardiogram showing holosystolic high velocity flow away from transducer.

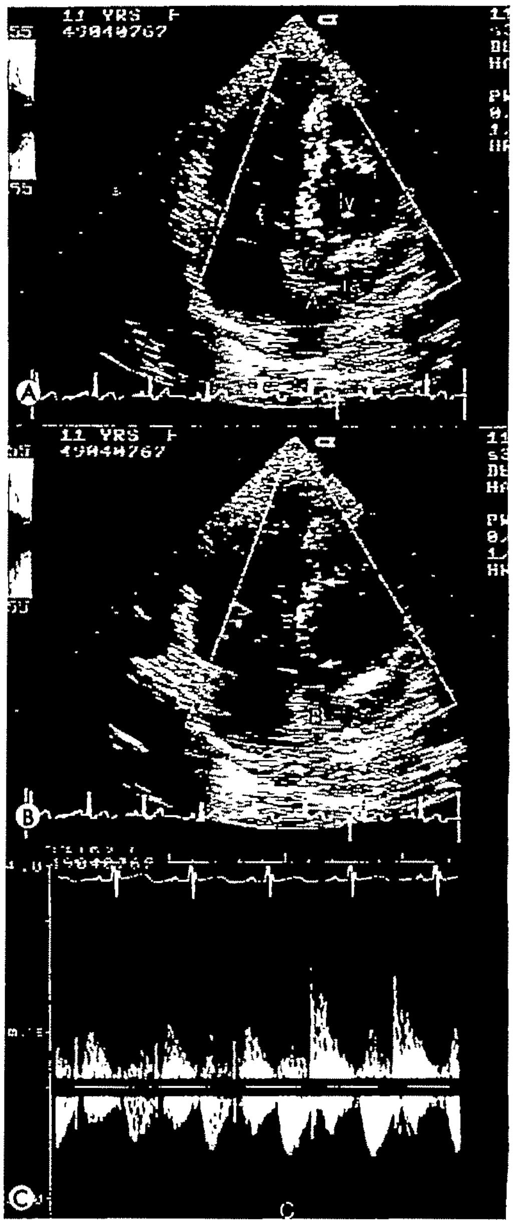

Figure 2 Colour flow Doppler imaging of aortic valve, four chamber view in case 7. (A) Early diastole. Note mosaic coloured flow signal. Arrows show the extent to which it extends below the aortic valve (ao). la, left atrium, lv, left ventricle. (B) Late diastole. Regurgitant signal persists identifying holodiastolic incompetence. Note that the appearance is now of minimal flow disturbance at the jet periphery with preservation of the central laminar core, effectively narrowing the jet width and possibly explaining the late high velocity signal drop out seen in panel C. (C) Continuous wave Doppler echocardiogram identifies high velocity regurgitant flow toward the transducer. The high velocity envelope becomes attenuated as late diastole is approached.

Colour flow Doppler imaging showed mitral regurgitation only in six children (cases 1, 2, 3, 8, 9, 11) and mitral and aortic regurgitation in four (cases 4, 5, 7, 10). The only child without evidence of valvar incompetence was case 6 who had recurrent fever and a circinate rash, thought by many observers to be erythema marginatum. Both symptoms lasted for roughly one month; rheumatic fever in this patient has been neither confirmed nor ruled out. Ten of 11 children therefore, in this study group had evidence of either mitral or mitral and aortic regurgitation with no auscultatory findings.

GROUP 1B

Figure 3 shows that of the preliminary group of 10 subjects,[1] seven had colour flow Doppler analysis 18 months to three years after the acute episode. Of the six children who had positive Doppler echocardiographs in the acute period, four continued to show incompetence of at least one valve and two had become completely normal; none had developed murmurs of mitral or aortic regurgitation. One child who showed no positive findings in the acute period was not followed up. Two other patients not now available to the study, were positive by Doppler echocardiography early in the quiescent period.

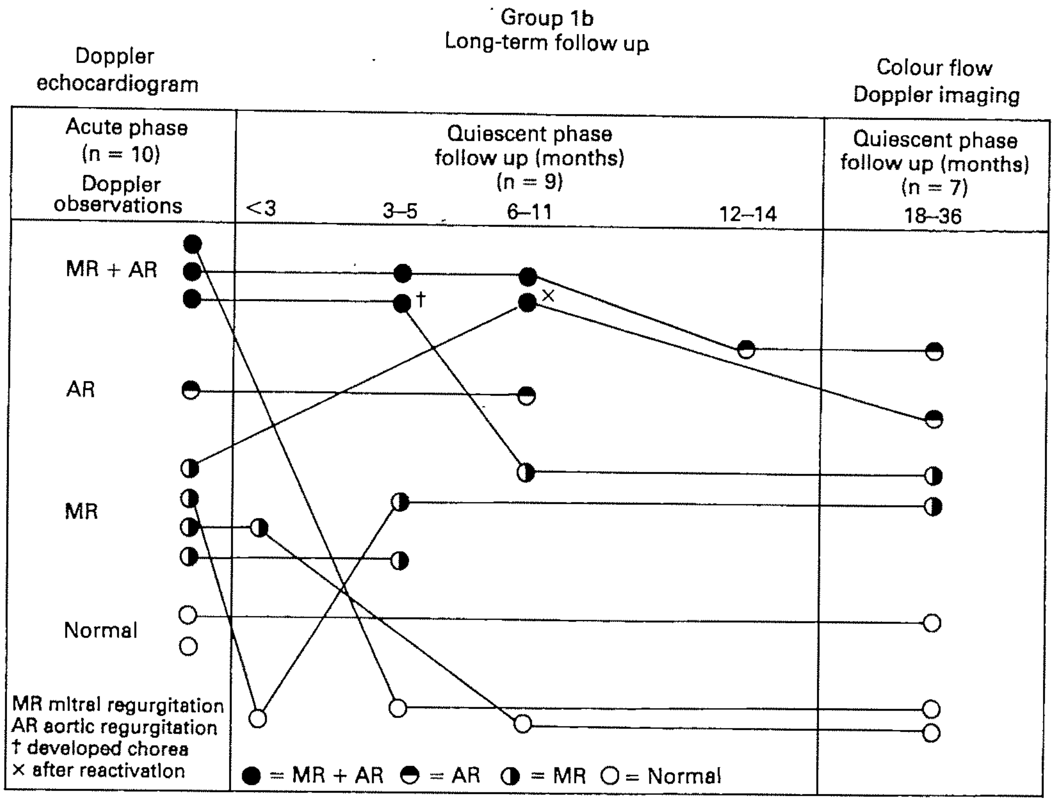

Figure 3 Long-term outcome of children with acute rheumatic fever without evident carditis. Four of the six children now undergoing follow up who showed Doppler echocardiographic evidence of valvar insufficiency in the acute period continued to have positive findings by colour flow Doppler 18 to 36 months later.

GROUP 2

Table 1 shows details of the eight children included in group 2, who were all considered to have auscultatory evidence of carditis. The group was similar in age range and sex to those in group 1a. The ranges of their prolongations of P R interval, acute phase reactants, and antistreptolysin O titres were also similar, as was their echocardiographically determined valvar involvement. It is noteworthy that colour flow Doppler analysis identified additional and clinically unsuspected valvar regurgitation in two of these children.

CONTROL PATIENTS (GROUPS 3 AND 4)

Table 2 shows details of groups 3 and 4. The children included in group 3 served as controls because they were shown eventually not to have rheumatic fever. Each of these seven children, who ranged in age from four to 11, had been admitted as possibly having acute rheumatic fever because of complaints and findings of arthritis or arthralgia. None of them showed evidence of regurgitation involving either the mitral or aortic valves. This finding was identical to that in the previous report.[1] The occurrence of trivial flow into the left atrium in presystole that persisted briefly into early systole in one of these children was considered to be physiological.

The seven children aged four and a half to 16 who make up group 4 were studied during their admission for indications not related to rheumatic fever. None of them showed mitral or aortic incompetence.

Discussion

The present study confirmed our preliminary findings that the addition of Doppler echocardiography gave useful diagnostic information.[1] We also found that the addition of colour flow

Table 2 Details of control patients

Group	*Indication for study (n)*	*ESR (mm/hr)/ASO (units)*	*Colour flow Doppler*
Group 3	Tendinitis (1)	50/200	0
(age range 4 – 11) (F3 M4)	Reactive polyarthritis (2)	25/<200	TR
		45/<200	Phys MR
	Non-specific arthralgia (1)	37/<200	0
	Monarticular arthritis (1)	20/<200	PR
	Anaphylactoid purpura (2)	90/NP	0
		55/<200 (1)	0
Group 4	Cardiac transplant (1)		0
(age range 4·5–16) (F4 M3)	Conduction abnormality (2)		0
	Obesity (1)	NP	0
	Cardiomegaly (2)		TR (2)
	Innocent murmur (1)		TR

NP, not performed; Phys MR, physiologic mitral regurgitation; PR, pulmonary regurgitation; TR, tricuspid regurgitation.

imaging identified the site of the valve regurgitation and was especially useful in the small number of children in whom a complete spectral envelope could not be obtained (fig 2). This small study group represents a considerable experience of acute rheumatic fever. We are aware of no other study which Doppler echocardiography and Doppler colour flow mapping were used to detect valvar regurgitation in children without clinical evidence of carditis. Both methods detected regurgitation in a high proportion of patients. Indeed, the combined findings of 18 out of 21 patients studied who had mitral, or aortic regurgitation, or both, in the acute period is noteworthy. These findings accord with those of other groups who used different methods of detection.[3,4]

Several groups have found mitral regurgitation by Doppler and colour flow imaging in normal children.[5-7] From the descriptions of these it is apparent that the findings are usually those of abbreviated regurgitant flow into the left atrium, which we have also found. This occurs early in systole, occasionally starting in presystole, and seems to be a physiological event seen more commonly in older people. If our guidelines for mitral regurgitation were strictly followed overdiagnosis of organic mitral regurgitation is highly unlikely. Recently published reports[5-7] and our own experience strongly suggest that non-organic (functional) mitral regurgitation does not produce holosystolic flow by Doppler echocardiography or colour flow imaging techniques. To our knowledge aortic regurgitation is not a normal finding.

These results have several implications for the diagnosis and management of patients with rheumatic fever. We believe that the colour flow Doppler findings should be added to the existing Jones criteria for diagnosis of acute rheumatic fever,[8] especially because of the difficulty encountered when the Jones criteria are not completely satisfied. Because under the colour flow Doppler conditions described here these regurgitant flow patterns are not present in normal children and young adults,[5-7] their presence when carditis is not clinically apparent should be of considerable value in the diagnosis of rheumatic fever. None of the control patients showed evidence of organic mitral or aortic regurgitation. As is usual, there was occasional tricuspid and pulmonary valvar regurgitation[5-7] in some of the controls as well as in several of the patients with rheumatic fever.

Some view the natural history of rheumatic fever when there is no clinical evidence of carditis as quite different and more favourable than when carditis is obvious.[9,10] The term mimetic[11] has been applied to each of these events suggesting reduced likelihood of valvar heart disease with recurrences of rheumatic fever when no carditis was obvious during the initial or subsequent bouts. The current findings however, indicate otherwise. They show that an appreciable number of these valves have been rendered incompetent regardless of the trivial nature of the findings, and many were still incompetent at follow up examination. To be more specific, these patients have valvar heart disease as a result of carditis that was not evident by the usual clinical means and this discovery is relevant to the perception of the natural history of pure rheumatic polyarthritis. Acute rheumatic fever without carditis is obviously not the benign entity that others have indicated, because it is nearly always accompanied by subclinical carditis, and the future of these patients is less certain than has been supposed.[9-11] This also applies to chorea without evident carditis.

Anatomical deformity aside, it may be that these valves become more vulnerable[12] to damage by a recurrence of infection. This possibility must be considered before measures to prevent rheumatic damage are relaxed.

We believe that the addition of colour flow Doppler echocardiography to the Jones criteria for acute rheumatic fever would improve the identification of patients with mitral or aortic valve disease who require lifelong prophylaxis against rheumatic fever but who have no clinical evidence of cardiac involvement.

1 Folger GM Jr, Hajar R. Doppler echocardiographic findings of mitral and aortic valvular regurgitation in children manifesting only rheumatic arthritis. *Am J Cardiol* 1989; 63:1278–80.

2 Markowitz M, Kuttner AG. *Rheumatic fever. Diagnosis management and prevention*. Philadelphia: WB Saunders, 1965:62–6.

3 Veasy LG, Wiedmeier SE, Orsmond GS, *et al*. Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 1987;316:421–7.

4 Steinfeld L, Ritter S, Rappaport H, Martinez E. Silent rheumatic mitral regurgitation unmasked by Doppler studies [abstract]. *Circulation* 1986;74 (suppl II):385.

5 Kostucki W, Vandenbossche J, Friart A, Englert M. Pulsed Doppler regurgitant flow patterns of normal valves. *Am J Cardiol* 1986;58:309–13.

6 Yoshida K, Yoshikawa J, Shakudo M, *et al*. Color Doppler evaluation of valvular regurgitation in normal subjects. *Circulation* 1988;78:840–7.

7 Berger M, Hecht SR, Van Tosh A, Lingam U. Pulsed and continuous wave Doppler echocardiographic assessment of valvular regurgitation in normal subjects. *J Am Coll Cardiol* 1989;13:1540–5.

8 Ad hoc committee to revise the Jones criteria (modified) of the council on rheumatic fever and congenital heart disease of the American Heart Association (1965). Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation* 1984;69:203–8.

9 Wenger NK, Leonard R, Bivins B. Acute rheumatic fever without carditis: a reappraisal. *Am J Cardiol* 1966;17: 142–3.

10 Committee on rheumatic fever and bacterial endocarditis of the Council on Cardiovascular Disease in the Young of the American Heart Association. Prevention of rheumatic fever. *Circulation* 1977;55:223–6.

11 Feinstein AR, Spagnuolo M. Mimetic features of rheumatic fever recurrences. *N Engl J Med* 1960;262:533–7.

12 Raizada V, Williams RC, Chopra P, *et al*. Tissue distribution of lymphocytes in reheumatic heart valves as defined by monoclonal anti-T cell antibodies. *Am J Med* 1983; 74:90–6.

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, 63, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, 325, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, 325, 303.

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Aortic valve regurgitation and the congenitally bicuspid aortic valve: a clinico-pathological correlation

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Abstract

***Objective*—To investigate the morphology of congenitally bicuspid aortic valves causing pure valve regurgitation.**

***Design*—A case series collected over five years.**

***Setting*—An academic hospital.**

***Patients and methods*—One hundred and forty eight excised congenitally bicuspid aortic valves. The morphological findings were correlated with sex, age, clinical history, and data on haemodynamic function before operation. Pure valve regurgitation was defined as grade 3–4/4 with a gradient less than 30 mm Hg. Aortic root dilatation was evaluated angiographically or echocardiographically or both.**

***Results*—Three types were recognised: valves that were purely bicuspid (23%), bicuspid valves with a raphe (34%), and valves with an additional indentation of the free edge of the conjoined cusp (43%). In 14 cases pure valve regurgitation was present. Dilatation of the aortic root was present in 47 cases. The relative risk for regurgitation when the aortic root was dilated (compared with no dilatation) was 3·99. The relative risk for valve regurgitation when there was indentation of the conjoined cusp (compared with no indentation) was 4·95. The mean age at operation in patients with pure regurgitation was 56 years, which is significantly younger ($p = 0{\cdot}0008$) than that of patients with a congenitally bicuspid valve with combined valve stenosis and regurgitation (64·7 years).**

***Conclusions*—Congenitally bicuspid aortic valves with a central indentation of the free edge of the conjoined cusp seem particularly likely to develop pure aortic valve regurgitation.**

Congenitally bicuspid aortic valves are not rare. The frequency of such valves in the population is estimated at approximately 1–2%.[1] The clinical course is usually dominated by acquired conditions such as infectious endocarditis and degenerative changes. Degenerative changes are an important cause of aortic valve stenosis requiring valve replacement.[2–4] Less is known, however, about the morphology of the congenitally bicuspid aortic valve that causes pure aortic valve regurgitation.

The present study was designed to investigate this particular aspect.

Patients and methods

We studied 148 patients (99 men, mean age 63·6 (31·3–85·7); 49 women, mean age 65·4 (34·9–81·0)) who had aortic valve replacement because they had what appeared to be a congenitally bicuspid valve. Patients with infectious endocarditis were excluded.

For each patient we noted the sex, age, clinical history, and haemodynamic variables assessed during preoperative cardiac catheterisation. Pure aortic valve regurgitation was defined as grade 3–4/4 with a gradient of less than 30 mm Hg measured during cardiac catheterisation.[5] Aortic root dilatation was assessed preoperatively during catheterisation in the usual qualitative manner,[6] or by means of M mode echocardiographic examination of the aorta in the parasternal long axis (> 37 mm).[7]

All 148 valves were fixed in 10% formaldehyde. Those valves excised in parts were carefully reconstructed. We paid particular attention to the shape of the leaflets and the presence or absence of a raphe. Calcifications, when present, were graded in a semiquantitative manner as slight (±), moderate (+) or severe (+ +). Calcifications were graded as slight if only a few calcified spots were identified. Valve calcification was regarded as severe when there were extensive deposits throughout both leaflets. Calcification between these extremes was graded as moderate.

STATISTICAL ANALYSIS

Differences between the recorded results where $p < 0{\cdot}05$ were regarded as statistically significant. Differences between proportional variables were tested with a χ^2 test and differences between continuous variables were tested by Student's *t* test. The study population was stratified according to valve morphology and the presence of aortic root dilatation. Risk ratios with 95% confidence intervals for aortic valve regurgitation were calculated according to Miettinen and Nurminen.[8]

Results

Three categories of valve morphology were identified (table 1 and figure). Firstly, valves with a raphe, which were classified as congenital bicuspid aortic valves with a conjoined cusp. There were 51 valves of this type (34%).

Secondly, a similar bicuspid valve with a distinct indentation of the free edge of the conjoined leaflet. There were 63 valves in this class (43%). Finally, in 34 congenitally bicuspid valves there was no detectable raphe (23%).

Of the 148 valves 143 showed some degree of calcification (table 1). The five valves without calcification all belonged to the group of (14) valves with pure regurgitation.

There was pure aortic valve regurgitation in 14 patients and dilatation of the aortic root in 47. Tables 1 and 2 show the correlation of valve dysfunction with each of the three different types of valve morphology and the relation between valve dysfunction and aortic root dilatation. Table 3 shows the data on valve morphology and the state of the aortic root in relation to the occurrence of pure aortic regurgitation.

We calculated the relative risk (RR) of pure aortic valve regurgitation when the aortic valve was indented. We also calculated the relative risk of valve regurgitation when the aortic root was dilated. Table 4 shows the results and the 95% confidence intervals.

Patients with pure valve regurgitation were significantly younger (mean 56 years) at operation ($p = 0{\cdot}0008$) than the group with congenitally bicuspid valves who did not have pure valve regurgitation (64·7 years). The numbers were too small to show any significant differences in age at operation in the subgroups.

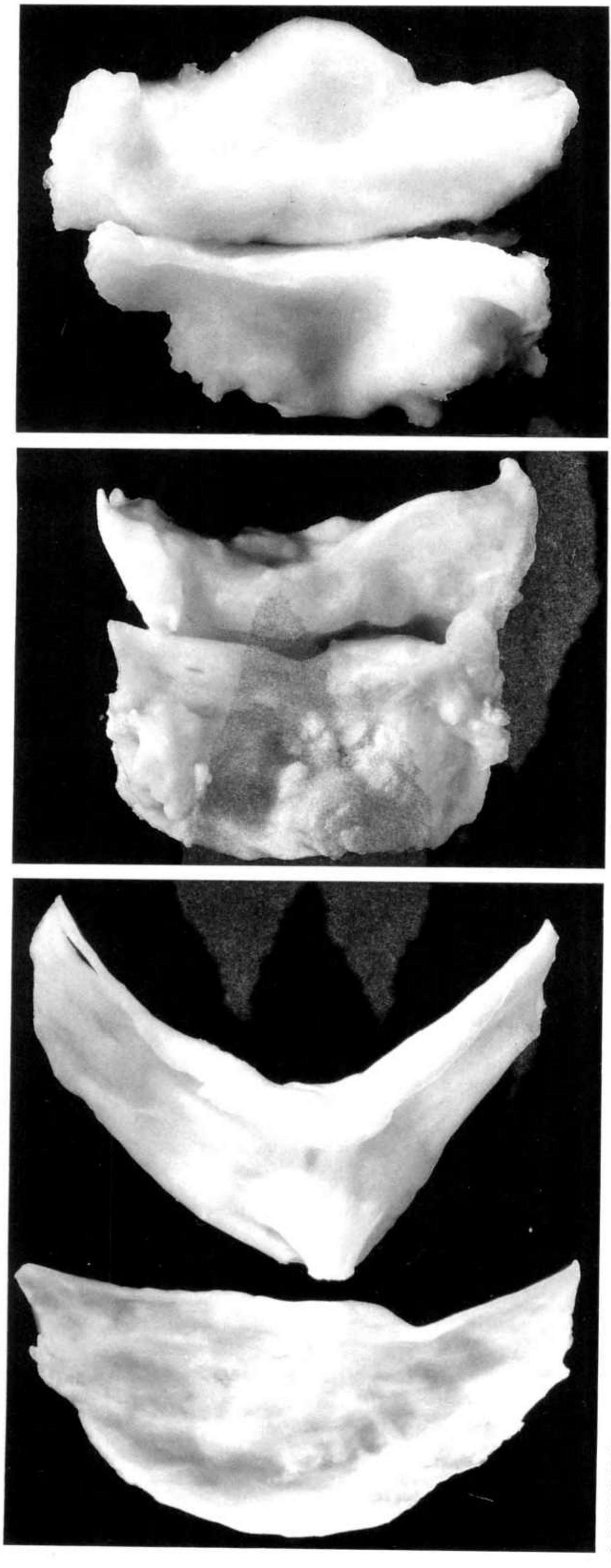
Discussion

Examination of 148 surgically resected congenitally bicuspid aortic valves showed three distinct groups: purely bicuspid valves (23%), bicuspid valves with a conjoined cusp containing a raphe (34%), and valves with a conjoined cusp and a distinct central indentation of the free edge (43%). This particular morphology has been reported as an important cause of isolated aortic regurgitation,[9 10] but its importance has not been further evaluated.

The present study shows that this particular type of valve morphology is likely to underly pure aortic valve regurgitation. Indeed, this was the case in 11 of 63 (17·5%) valves in this category, in contrast to only three (3·5%) out of 85 valves without such an indentation. The underlying mechanism almost certainly relates to the fact that the peculiar morphology interferes with the proper coaptation of the valve cusps, particularly once degenerative age related changes make the valve leaflets less mobile.

The relative risk of valve regurgitation was significantly increased when a congenitally bicuspid valve was indented, (table 4).

Five of the 14 valves associated with pure valve regurgitation showed no gross calcifications, whereas there was slight to moderate



(Top) Gross appearance of a congenitally bicuspid aortic valve with degenerative changes; (middle) a congenitally bicuspid aortic valve with a raphe and extensive calcifications; and (bottom) a degeneratively changed congenitally bicuspid aortic valve with an indentation of the conjoined cusp, which also contains a raphe. The rolled free edge of the conjoined cusp is a clear expression of long term serious valve regurgitation.

Table 1 Relation between valve dysfunction and valve morphology

Morphology	*Pure regurgitation*	*Stenosis/regurgitation*	*Total*
Bicuspid	1	33 (7+; 26++)	34
Bicuspid with raphe	2 (1±; 1+)	49 (1±; 7+; 41++)	51
Bicuspid with raphe and indentation	11 (3±; 3+; 1++)	52 (14+; 38++)	63

Calcification: ±, slight; +, moderate; ++, severe.

Table 2 Relation between valve dysfunction and the state of the aortic root

Root	*Pure regurgitation*	*Stenosis/ regurgitation*	*Total*
Normal	5	96	101
Abnormal	9	38	47

Table 4 Relative risk of pure valve regurgitation

	No	*Relative risk (95% confidence interval)*
Bicuspid/raphe/ indentation	63	4·95 (1·6 to 16)
Abnormal aortic root	46	3·99 (1·5 to 11)

calcification in the remaining nine valves. These observations contrast with the moderate to severe calcification in all valves associated with combined stenosis and insufficiency. The age at operation may be a factor but it is tempting to attribute this finding to haemodynamic differences.

Although prolapse of valve leaflets is widely accepted as a cause of regurgitation where the aortic valve is congenitally bicuspid,[10 11] none of our patients showed evidence of prolapse at the preoperative examination. On the other hand, dilatation of the aortic root is known to be an important associated anomaly.[9-11] Although the precise pathogenetic mechanisms are not yet fully understood, degenerative aortic medial disease is likely to be the underlying disorder. Whether this is congenital and part of a syndrome[12] or a secondary effect caused by altered haemodynamic function affecting the ventriculoaortic junction remains to be established. In our study there was dilatation of the aortic root in 32% of the cases. The relative risk of aortic valve insufficiency was significantly higher when a congenitally bicuspid valve was associated with aortic root dilatation (tables 2 and 4). Our results suggest that individuals with an abnormally wide aortic root and a bicuspid valve showing an indentation are more liable to develop pure valve regurgitation (30% of that subgroup). The numbers, however, are too small to regard these findings as more than highly suggestive.

Table 3 Valve morphology and the state of the aortic root in relation to the occurrence of pure aortic regurgitation (total number of each type of valve is shown in parentheses)

Aortic root	*Bicuspid*	*Bicuspid/raphe*	*Bicuspid/raphe/ indentation*	*Total*
Normal	0 (21)	0 (37)	5 (43)	5 (101)
Abnormal	1 (13)	2 (14)	6 (20)	9 (47)
Total	1 (34)	2 (51)	11 (63)	14 (148)

The mean age at which valve replacement is performed in patients with a congenitally bicuspid aortic valve is significantly lower in those with pure valve regurgitation. In this study we identified aortic valves with an indentation of the conjoined cusp as an important cause of valve regurgitation—the clinical importance of this morphological type of valve is evident.

1 Edwards WD. Surgical pathology of the aortic valve. In: Waller BF, ed. *Pathology of the heart and great vessels*. New York: Churchill Livingston, 1980:43–100.

2 Subramanian R, Olson LJ, Edwards WD. Surgical pathology of pure aortic stenosis: a study of 374 cases. *Mayo Clin Proc* 1984;59:683–90.

3 Peterson MD, Roach RM, Edwards JE. Types of aortic stenosis in surgically removed valves. *Arch Pathol Lab Med* 1985;109:829–32.

4 Passik CS, Ackermann DM, Pluth JR, Edwards WD. Temporal changes in the causes of aortic stenosis: a surgical pathologic study of 646 cases. *Mayo Clin Proc* 1987;62:119–23.

5 Basta LL, Raines D, Najjar S, Kioschos JM. Clinical, haemodynamic, and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. *Br Heart J* 1975;37:150–7.

6 Grossman W, Baim DS, eds. *Cardiac catheterization, angiography and intervention*. Philadelphia: Lea and Febiger, 1991:244–64.

7 Feigenbaum H, ed. *Echocardiography*. Philadelphia: Lea and Febiger, 1986:622.

8 Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985;4:213–26.

9 Guiney TE, Davies MJ, Parker DJ, Leech GJ, Leatham A. The aetiology and course of isolated severe aortic regurgitation: a clinical, pathological, and echocardiographic study. *Br Heart J* 1987;58:358–68.

10 Davies MJ. *Pathology of cardiac valves*. London: Butterworths, 1980:37–61.

11 Olson LJ, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: a study of 225 cases. *Mayo Clin Proc* 1984;59:835–41.

12 Lindsay J. Coarctation of the aorta, bicuspid aortic valves and abnormal ascending aortic wall. *Am J Cardiol* 1988;61:182–4.

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Can mitral regurgitation after balloon dilatation of the mitral valve be predicted?

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Abstract

***Objective*—To determine which factors predict the occurrence of mitral regurgitation after balloon dilatation of the mitral valve for rheumatic stenosis.**

***Design*—Analysis of a case series of patients with rheumatic mitral valve stenosis who had had successful balloon dilatation of the mitral valve.**

***Setting*—A tertiary care centre with an experience of over 150 balloon dilatations of the mitral valve.**

***Patients*—70 young patients with non-calcified rheumatic mitral stenosis, who had undergone successful balloon dilatation of the mitral valve. No patient had mitral regurgitation or atrial fibrillation before dilatation.**

***Intervention*—Dilatation of the mitral valve by the transvenous, transatrial double balloon technique.**

***Main outcome measure*—Development of mitral regurgitation after balloon dilatation of the mitral valve and its relation to age, mitral valve area before dilatation and after dilatation, the degree of mitral subvalvar pathology, and the size of balloon used for dilatation.**

***Results* In 10 patients (14%) mitral regurgitation developed after balloon dilatation of the mitral valve. No statistically significant differences were found between patients who did not develop regurgitation and those who did in terms of age (mean (SD)) (19·9 (6·46) *v* 19·4 (5·5)), mitral valve area before dilatation (1·05 (0·33) *v* 0·94 (0·4) cm^2) and after dilatation (2·52 (1·06) *v* 2·45 (1·1) cm^2), mitral subvalvar pathology assessed by the mitral subvalvar distance ratio (0·116 (0·03) *v* 0·118 (2·32), or balloon diameter corrected for body surface area (21·37 (3·5) *v* 20·57 (2·32) mm/m^2.**

***Conclusions*—In this subset of children and young adults with non-calcified mitral stenosis, none of the morphological, technical, or patient characteristics studied predicted the development of mitral regurgitation after balloon dilatation. The low incidence of mitral regurgitation may have reduced the discriminatory power of this study. None the less, the means and standard deviation for each factor in each group suggest that even in a larger sample size the variables would have little predictive capacity.**

Balloon dilatation of the mitral valve has emerged as an effective non-surgical technique for the treatment of rheumatic mitral stenosis.[1-3] Mitral regurgitation after balloon dilatation is reported to occur in about 20–53% of patients.[4-6] Though it is mild in most, this procedure-induced regurgitation has led to concern about the safety of dilatation. We reviewed a series of 70 patients who had balloon dilatation of the mitral valve at our hospital to determine whether certain important technical factors or features of valve morphology predicted the development of mitral regurgitation after balloon dilatation.

Patients and methods

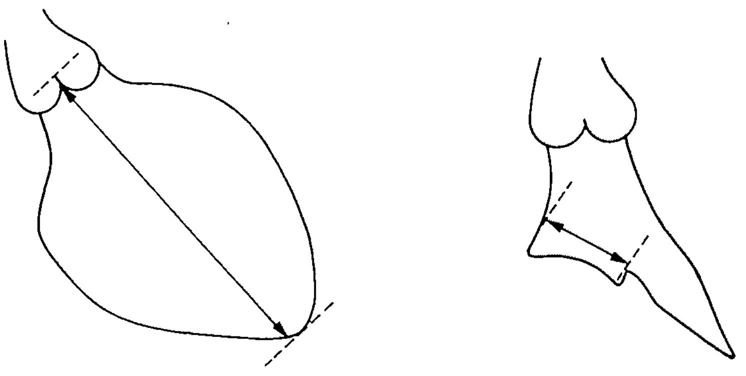
We reviewed data on 70 patients with pure rheumatic mitral stenosis (25 male and 45 female, aged 10–30 (mean (SD) 19·2 (6·4) years) who had balloon dilatation of the mitral valve. All patients underwent percutaneous balloon dilatation of the mitral valve by the anterograde, trans-septal route by the double balloon technique described earlier.[4] Mitral regurgitation was assessed before and after the procedure by left ventricular cineangiogram in 30° right anterior oblique view. The degree of mitral regurgitation was graded as 1+ to 4+ by the method described by Grossman.[7] The following factors were analysed retrospectively to examine their relation to mitral regurgitation induced by the procedure: (*a*) age, (*b*) severity of mitral stenosis before balloon dilatation, (*c*) mitral valve area achieved after dilatation, (*d*) effective balloon diameter/m^2 of body surface area, and (*e*) degree of mitral subvalvar pathology. Mitral subvalvar pathology was assessed on the left ventricular cineangiogram and expressed as the mitral subvalvar distance ratio (the ratio of the distance from the mitral valve to the tip of the papillary muscle in end diastole to the distance from the aortic valve to the left ventricular apex in end diastole[8] (figure).

STATISTICAL ANALYSIS

The distribution of the various factors studied in patients in whom mitral regurgitation developed after balloon dilatation of the mitral valve and in patients in whom it did not were compared by Students χ^2 test. A p value of $<0·05$ was regarded as statistically significant.

Results

All patients were in sinus rhythm and had moderate to severe mitral stenosis (valve area 0·5–1·5 cm^2, mean (SD) 0·96 (0·35) cm^2) before


Aortic valve to
left ventricular apex in diastole
(AV–LVA)
Mitral valve to
papillary muscle tip in systole
(MV–PM)

$$\text{Mitral subvalvar distance ratio (MSDR)} = \frac{\text{(MV–PM)}}{\text{(AV–LVA)}}$$

Method for determining the mitral subvalvar distance ratio.

Characteristics (mean (SD)) of patients with and without mitral regurgitation (MR) after balloon dilatation

Variable	*No MR (n = 60)*	*MR (n = 10)*
Age	19·9 (6·46)	19·4 (5·5)
MVA before (cm²)	1·05 (0·33)	0·94 (0·4)
MVA after (cm²)	2·52 (1·06)	2·45 (1·1)
Distance ratio	0·116 (0·03)	0·118 (0·02)
EDB/BSA (mm/m²)	21·37 (3·5)	20·75 (2·32)

MVA, mitral valve area; EBD, effective balloon diameter; BSA, body surface area.

dilatation. After dilatation the mitral valve area increased significantly ($p < 0{\cdot}001$) to 1·4–4·08 cm² (mean (SD) 2·3 (0·83) cm²).

MITRAL REGURGITATION

No patient had mitral regurgitation before balloon dilatation. After dilatation mitral regurgitation was seen in 10 (14%) patients. Mitral regurgitation was 1+ in eight patients and 2+ in two patients. Mitral regurgitation was well tolerated haemodynamically in all 10 patients and no patient required mitral valve replacement for this complication.

RELATION OF MITRAL REGURGITATION TO VARIOUS FACTORS

A comparison of patients with procedure-induced mitral regurgitation (n = 10) and those without (n = 60) showed no statistically significant difference for any of the variables assessed (table).

Discussion

Mitral regurgitation caused by balloon dilatation is seen in about 20% of patients[9] and is an important potential complication of the procedure. The patients in our study were much younger than those in other large series, and new mitral regurgitation in younger patients may be expected to be more harmful in the long term. This is why we thought it important to determine the frequency of mitral regurgitation after balloon dilatation, so that we could change patient selection and/or the technique if necessary.

We found new regurgitation in 14% of our patients. This incidence is slightly lower than that reported by Abascal *et al*[5] and Nobuyoshi *et al*[6]; the difference may be explained by the different age group studied and the absence of calcified mitral stenosis in our study. As in the other studies, most instances of mitral regurgitation after balloon dilatation were mild. Not one had 3+ or 4+ mitral regurgitation. We did not find any significant difference in the age, severity of mitral stenosis before dilatation, mitral valve area achieved, balloon size used, or the extent of mitral subvalvar pathology between patients in whom mitral regurgitation developed and those in whom it did not. Abascal *et al* also found no association between the production or worsening of regurgitation and valve and subvalvar morphology, balloon size, age, sex, initial mitral valve area or increase in mitral valve area or both.[5] Nobuyoshi *et al*, however, reported that mitral regurgitation was less frequent and less severe in patients with a pliable valve, while in patients with semipliable or rigid valves the incidence and severity of clinically important mitral regurgitation increased.[6] Most of our patients had moderate degree of subvalvar pathology — and, therefore, the mitral valve morphology may have been significantly different from that in the study by Nobuyoshi *et al*. Vahanian *et al* also reported that severe (but not mild or moderate) mitral regurgitation after balloon dilatation correlated with anatomical features such as calcified valves and extensive subvalvar disease.[10] None of our patients had calcified mitral stenosis nor did balloon dilatation cause any cases of severe mitral regurgitation.

We did not identify any statistically significant differences between the means of the measured technical or morphological variables in patients with mitral regurgitation after balloon dilatation and those without. Because only 10 patients developed mitral regurgitation the power of these tests was low. However, the means (SD) in the table suggest that even if a significant difference was found for any of the variables in a larger sample there would still be substantial overlap between the two distributions and hence the variable would have little predictive capacity.

1 Roy SB, Bhatia ML, Lorazo EJ, Ramalingaswami V. Juvenile mitral stenosis in India. *Lancet* 1963;ii:1193–5.
2 Kraus F, Dacihn S, Friedricks W, Ruolf C, Halld RW. Haemodynamic results of mitral valvuloplasty compared with commissurotomy and valve replacement. *Circulation* 1987;76 (suppl IV):IV–89.
3 Lock JE, Khalilllah M, Srivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;313:1515–8.
4 Arora R, Nair M, Rajagopal S, Sethi KK, Mohan JC, Nigam M, *et al*. Percutaneous mitral valvuloplasty in children and young adults with rheumatic mitral stenosis. *Am Heart J* 1989;118:883–7.
5 Abascal VM, Wilkins GT, Choong CY, Bloc PC, Palacios IF, Weyman AE. Mitral regurgitation after percutaneous balloon mitral valvuloplasty in adults; evaluation by pulsed Doppler echocardiography. *J Am Coll Cardiol* 1988;11:2:257–63.

6 Nobuyoshi M, Hamasaki N, Kimiura T, Nosaka H, Yokoi H, Yasumoto H, *et al.* Indications, complications and short term clinical outcome of percutaneous transvenous mitral commissurotomy. *Circulation* 1989;80:4:782–92.

7 Grossman W. Profiles in valvular heart disease. In: Grossman W, ed. *Cardiac catheterisation and angiography.* 3rd ed. Philadelphia: Lea & Fabiger, 1986:365–6.

8 Akins CW, Kirklin JK, Block PC, Buckley MJ, Austen WG. Preoperative evaluation of subvalvular fibrosis in mitral stenosis. A predictive factor in conservative 3 Vs replacement surgical therapy. *Circulation* 1979 (suppl I): 71–6.

9 Abascal VM, Wilkins G, Choong CY, Thomas JD, Palacios IF, Block PC, *et al.* Echocardiographic evaluation of mitral valve structure and function of patients followed for at least 6 months after percutaneous balloon mitral valvuloplasty. *J Am Coll Cardiol* 1988;12:606–15.

10 Vahanian A, Michel PL, Cormier B, Viloux B, Michel X, Slama M, *et al.* Results of percutaneous mitral commissurotomy in 200 patients. *Am J Cardiol* 1989;63:847–52.

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Histological changes in the aortic valve after balloon dilatation: evidence for a delayed healing process

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Abstract

Objective—**To investigate whether balloon dilatation of the aortic valve induces long-term macroscopic or histological changes or both to explain the restenosis process.**

Design—**Prospective study of 39 consecutive patients. Sixteen later (mean (SD) 12 (10) months) required operation. This non-randomised subgroup was compared with 10 patients who had aortic valve replacement without prior dilatation.**

Setting—**University cardiology and cardiac surgery centre and pathology department.**

Patients—**16 patients who had aortic valve replacement because of failure of or restenosis after balloon dilatation of the aortic valve. Twelve resected valves were examined.**

Interventions—**Percutaneous balloon dilatation of the aortic valve (maximal balloon size: trefoil 3 × 12 mm balloon or bifoil 2 × 19 mm balloon) and surgical inspection before excision of the aortic valve leaflets during open-chest aortic valve replacement. Fixation, decalcification, and staining for histology.**

Main outcome measures—**Presence of long-term pathological changes in the resected valve and their relation to restenosis after balloon dilatation.**

Results—**Macroscopically the previously dilated valves were indistinguishable from valves from the patients who had valve replacement only. Microscopically, the dilated aortic valves showed areas of young scar tissue that were not seen in a control group of surgically excised stenotic aortic valves. This persistent scarring reaction was seen around small tears or lacerations of the collagenous valve stroma, fractures in calcified areas, and splits in commissures. Young scar tissue without collagenisation was still present 24 months after dilatation.**

Conclusion—**Organisation and collagenisation of scar tissue develops slowly after balloon dilatation of the aortic valve. This prolonged scarring reaction may explain the late development of restenosis in some patients.**

Balloon dilatation of the aortic valve has been advocated by several groups as an alternative to aortic valve replacement in patients at high surgical risk or as an intermediate procedure to improve left ventricular function before elective aortic valve replacement.[1-4] Recurrence rates, whether clinically defined or assessed invasively or non-invasively, are high (24–67%).[5-9] This high restenosis rate leads to many subsequent procedures. Two recently published series reported reinterventions in about a quarter of the patients after a mean follow up of six months. A further quarter did not survive this follow up period.[5 7] The immediate effect of balloon dilatation on calcific aortic valves has been extensively studied during in vitro and intraoperative studies.[10 11] Little is known about the effects of balloon dilatation at a microscopic level or the sequence of any histological changes with time.[9 12 13] To examine the frequency and extent of these changes after dilatation we studied 12 previously dilated aortic valves excised during valve replacement and compared the histological findings with those in resected non-dilated aortic valves from patients of a similar age.

Patients and methods

From March 1986 to December 1989, 39 elderly patients underwent percutaneous balloon dilatation of the aortic valve. Sixteen of these patients later underwent aortic valve replacement. Table 1 shows the characteristics of all patients undergoing aortic valve dilatation and of the group who subsequently had aortic valve replacement.

Table 1 Characteristics (mean (SD)) of all patients undergoing balloon dilatation of the aortic valve (BD) and of patients with and without subsequent aortic valve replacement (AVR)

Characteristic	*BD*	*AVR*	*non AVR*
Number	39	16	19
M / F	15/24	6/10	7/12
Mean age (y) (range)	75·1 (58–88)	72·1 (63–85)	77·3 (58–88)
Left ventricular ejection fraction:			
⩾0·55	22	10	12
0·40–0·54	6	2	4
0·20–0·39	5	1	2
⩽0·19	4	1	1
Not-assessed	2	2	0
Aortic valve area before dilatation (cm^2)	0·47 (0·14)	0·51 (0·11)	0·45 (0·15)
Aortic valve area after dilatation (cm^2)	0·75 (0·19)	0·75 (0·15)	0·74 (0·21)
Aortic valve area increase (%)	63·0 (38·0)	52·0 (32·0)	64·0 (33·0)

Table 2 Clinical characteristics and outcome of balloon dilatation of the aortic valve in 16 patients who subsequently had aortic valve replacement

No	Age	Sex	Maximal balloon size (mm)	AVA (cm²) B	AVA (cm²) A	% AVA increase	Interval between dilatation and operation (mnth)
1	63	M	20	0·59	0·81	37	13
2	76	M	20	0·53	0·88	66	6
3	74	F	3 × 12	0·34	0·36	6	10
4	65	F	3 × 12	0·49	0·57	16	1
5	75	M	20	0·71	0·96	35	7
6	64	M	3 × 12	0·37	0·64	73	9
7	72	F	19	0·66	AI grade III		6 days
8	74	F	3 × 12	0·46	0·70	52	8
9	85	F	2 × 19	0·57	0·71	30	3
10	73	M	3 × 12	0·59	NA		13
11	64	F	20	0·33	0·80	142	36
12	75	M	20	0·57	0·95	67	24
13	75	F	3 × 12	0·39	0·71	82	27
14	72	F	15	0·62	0·85	37	20
15	71	F	23	0·41	0·71	73	6
16	77	F	3 × 12	0·53	0·78	47	13

A, after; AI, aortic insufficiency; AVA, aortic valve area; B, before dilatation; NA, not assessed.

DILATATION PROCEDURE

All procedures were performed with a percutaneous femoral approach with Schneider-Shiley balloons and introducers (Zurich, Switzerland). After baseline values were recorded the aortic valve area was calculated on line by measuring the mean transvalvar pressure gradient and aortic valve flow. Balloons of increasing size were then introduced to increase the aortic valve area by at least 50% (the maximal balloon diameter in the first 29 patients was trefoil 3 × 12 mm balloon and in the last 10 patients it was bifoil 2 × 19 mm balloon). In the last 22 patients a 100 cm long 16·5 French introducer was used.[14 15] A successful procedure was arbitrarily defined as an increase in aortic valve area of at least 25%, without death or major complications necessitating urgent surgery. Table 1 summarises the haemodynamic data before and after valve dilatation. In five patients the valve area could not be calculated after the procedure (two patients died after the first balloon inflation, two patients had considerable aortic regurgitation after dilatation that precluded calculation of the aortic valve area, while in a fifth patient data were not recorded because of neurological complications). Restenosis was defined as a clinical recurrence of symptoms with either a return of maximal aortic valve flow velocity to predilatation values on Doppler flow measurements or an invasively measured increase in aortic valve area of < 25%.

MORTALITY AND PROCEDURAL FAILURE

Four patients died within 28 days after balloon dilatation. Two patients in severe heart failure died during the procedure after the first balloon inflation. In a third patient, also with severe failure, the procedure was successful but he died one week later of progressive heart failure. The fourth patient had signs of aortic base dissection after inflation of a bifoil 2 × 19 mm balloon and died 24 hours later. One patient was operated upon within one week of the procedure because of severe aortic regurgitation (table 2, case 7).

Table 3 Peroperative findings and early postoperative course after inadequate balloon dilatation and subsequent aortic valve replacement

No	Valve anatomy	Commissural fusion	Calcifications	Tearing of leaflets
1	B	No	3+	No
2	B	No	3+	No
3	B	No	3+	No
4	T	No	3+	No
5	B	No	3+	No
6	B	No	2+	No
7	B/T	Yes/No	2+	Yes
8	T	Yes	3+	No
9	T	No	3+	No
10	B	No	3+	No
11	T	No	3+	No
12	T	No	3+	No
13	NA	NA	3+	NA
14	T	No	3+	No
15	T	No	3+	No
16	NA	NA	3+	NA

B, bicuspid aortic valve; +, tricuspid aortic valve; NA, not assessed.

Table 4 Histological findings in 12 excised aortic valves operated after percutaneous balloon dilatation of the aortic valve

Patient	Interval (mnth)	Operative indication	Collagenous stroma	Calcification	Bone formation	Pre-existing pathology: Superficial fibrin deposits	Pre-existing pathology: Superficial haemorrhages	Young scar in collagenous stroma
2	6	R	++	++	+	++	–	+
3	9	F	++	++	–	–	–	++
4	3 weeks	F	++	++	–	–	–	–
5	6	R	++	++	+	–	+	++
6	9	R	++	++	+	–	+	++
7	6 days	AI	++	++	–	–	–	+++
8	9	R	++	++	+	–	–	++ with sealed commissure
9	2	R	++	++	–	+	+	+
10	13	R/F?	++	++	–	–	+	+ superficial
11	36	R	++	++	–	–	+	–
12	24	R	++	++	–	+	+	++
15	6	R	++	++	–	–	–	++

AI, aortic valve insufficiency; F, dilatation failure; R, restenosis.

The procedure was considered to be unsuccessful in four patients because the valve area had increased by less than 25% after dilatation. Two of these patients subsequently had surgery (table 2, cases 3 and 4). One was operated upon within one month, the other experienced some relief of symptoms and was operated upon 10 months later. Of the other two with failed procedures, one died 19 months after the procedure, while the last patient was in validity class II (New York Heart Association) six months after valve dilatation. Of the remaining 30 patients, 13 had surgery because of clinical restenosis. Table 2 shows the haemodynamic and clinical details of the patients who had surgery.

FOLLOW UP OF NON-SURGICAL PATIENTS

Eight patients died during follow up. Death occurred at a mean (SD) of 15 (5) months after dilatation. Eleven patients were alive after a single dilatation procedure at a mean follow up of 23 (12) months.

SURGICAL PROCEDURE

All 14 patients operated upon in our hospital were treated according to the same standard surgical protocol. After incision of the aortic root we paid special attention to the macroscopic inspection of the previously dilated valve. We specifically looked for laceration of the valve leaflets, fracture of calcific deposits, and rupture of previously fused commissures. The underlying valve anatomy was established as uni, bi or tri cuspid. The amount of calcification was scored as + to +++ indicating minimal, moderate, or extensive involvement. After inspection the valve leaflets from 12 patients were excised and stored for microscopic examination.

HISTOLOGICAL TECHNIQUE

The fragments resected from patients 2 to 12 and 15 were fixed in 10% formalin and decalcified in rapid bone decalcifier (RDO, Dupage Kinetic Laboratories Inc, Plainfield, USA). After a routine paraffin processing cycle 5 μm sections were stained with haematoxylin-eosin and elastic van Gieson stain.

Results

MACROSCOPIC EXAMINATION

Table 3 shows the gross intraoperative anatomical findings in the 16 surgical patients. The aortic valve was bicuspid in six patients and tricuspid in seven patients. In one patient we were uncertain how many cusps were present. In two patients who had surgery in another hospital and one patient who underwent surgical valvuloplasty the aortic valve was not available for analysis (cases 13, 16 and 14). Macroscopic findings attributable to the previous valve dilatation were seen in only one patient (case 7, table 3). In this patient the valve was composed of a posteriorly situated thickened and heavily calcified cusp and of a less calcified anterior cusp (probably a fusion of the left and right coronary cusps). Balloon dilatation had lacerated (7 mm) the right side of the anterior cusp from the aortic wall. Because the posterior cusp was rigid, the radial balloon force was probably exerted more strongly on the more pliable cusp. Fracturing of calcific deposits was not grossly evident in any cases.

Pathology as result of valvuloplasty				
Young scar in calcified nodule	*Calcium fragments in scar*	*Iron loaden macrophages*	*Haemorrhages deep in stroma*	*Fibrin deep in stroma*
−	+	−	+	+
−	+ + histiocytic infiltrate	−	−	−
−	+ +	−	+	+
−	+ +	+	−	−
+ +	+	−	+	−
+ +	+ +	−	−	−
+ +	+ +	+	−	+
+	−	−	−	+
+ superficial	+	−	−	−
−	−	−	−	−
+	+ +	−	−	−
+	+ +	−	−	−

MICROSCOPIC EXAMINATION

Dilated valves

All the valves (table 4) showed the usual histological features of calcific aortic stenosis.[16] In two patients there was degenerative bone formation in the calcifications. In 11 of the 12 patients young scar tissue (consisting of a rather cell-rich pattern of fibroblasts, capillaries, and an inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes) was present. This scar tissue seemed to fill up the small tears and lacerations in the dense collagenous tissue stroma (11 patients) (fig 1A) and the fractures in the calcified nodules (seven patients) (fig 1B). Fragments of calcium embedded in the young scar tissue were seen in 10 patients (fig 1C). In one patient a commissure was re-sealed with recent scar tissue. Haemorrhages and fibrin within the valve stroma were seen in six patients, while superficial fibrin deposits and haemorrhages were seen in all patients. Only one patient showed the basic pathology of calcified aortic stenosis without recent scar tissue. However, this patient was operated upon 36 months after dilatation and by that time the scar tissue may have been completely organised. There was no clear difference in histological appearance between the successfully and the two non-successfully dilated patients, though one of the non-successfully dilated patients (case 3) showed an extensive histiocytic reaction around severely fragmented calcifications as well as young scar tissue in the collagenous valve stroma. The second patient (case 4) only showed scar tissue between fragmented calcifications.

Control valves

We examined a control group of 10 patients undergoing aortic valve replacement because of critical calcific aortic stenosis which was of similar age and sex distribution and gross macroscopic changes as the dilated group. Macroscopically the valves were indistinguishable from those of the dilated group. Histological examination showed superficial fibrin deposits, small haemorrhages, and iron-loaden macrophages in the subendothelium of

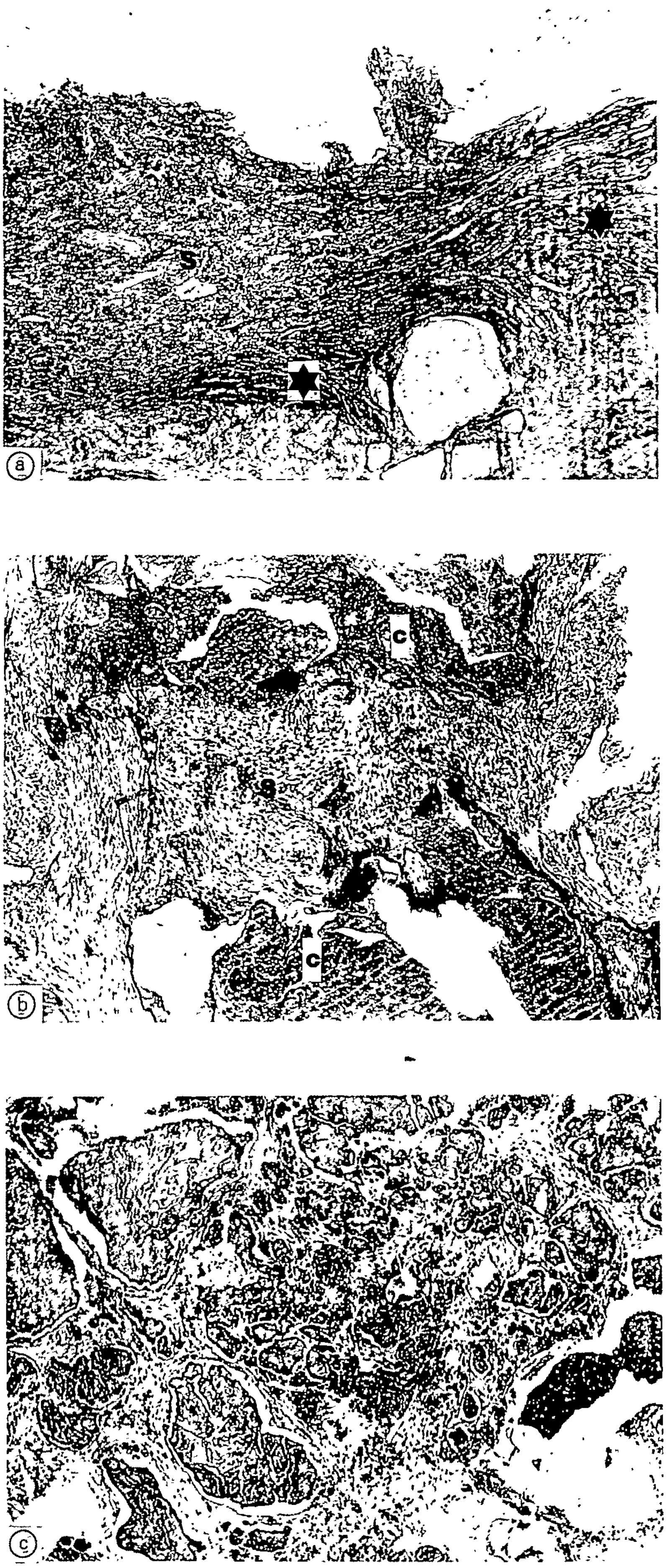

Figure Histological appearance of a segment of aortic valve leaflet after balloon dilatation. (A) Small laceration in the dense collagenous tissue stroma (*), filled with scar tissue (S). (B) Scar tissue (S) filling a fractured calcified nodule (C). (C) Calcium fragments embedded in young scar tissue.

valves from the control group. Although lymphocytes, plasma cells, and capillaries were present in the looser connective tissue stroma surrounding the dense collagenous stroma in some patients, none of the control valves showed the areas of young scar tissue seen in the patients treated with balloon dilatation.

Discussion

Whatever the initial mechanism, the underlying pathology of calcific aortic stenosis in the elderly is severe fibrosis and considerable calcifications of the valve leaflets occasionally associated with commissural fusion. These pathological changes render the valve rigid and immobile.[16]

As evident from our study and other published reports[10-12 17] the mechanisms of successful percutaneous balloon dilatation of the aortic valve are (*a*) cleavage or laceration of the dense collagenous valve stroma, (*b*) fracture and/or fragmentation of calcifications, and (*c*) separation of fused commissures.

It seems that the final outcome of balloon dilatation mainly depends on the severity of the underlying pathological abnormalities in the valve and the extent of the injury created by the balloon. In the two patients who had insufficient dilatation procedures with an increase of the aortic valve area of less than 25% we did indeed see some injury to the valve leaflets, but apparently it was not extensive enough. Commeau *et al* reported a similar finding in an intraoperative study.[9] They noticed that when the valve was extensively calcified there was no grossly obvious effect of dilatation. None the less, in one of our patients severe damage to the valve (a complete tear of a valve leaflet from the aortic wall) caused severe aortic regurgitation.

Injury to the aortic valve seems to be followed by scarring. We and others found that small tears or lacerations in the collagenous valve stroma, fractures in calcifications, and splits between commissures were filled up with young scar tissue.[12 17] Scar formation should be recognised as a possible mechanism for restenosis.[12 13] Indeed, development, organisation, and collagenisation of the young scar tissue in the tears and fractures in the valve will ultimately restore the valve's immobility and lead to restenosis. In addition, it seems from our study that organisation and collagenisation of the scar tissue in these valves takes longer than in other tissues. We saw non-collagenous scar tissue in the valves 24 months after dilatation: normally a scar is completely organised and collagenised within six weeks. The lack of a direct vascular supply to the valve leaflets may explain this prolonged process of repair, which resembles the slowly progressive inflammatory reaction of the chronic endocarditis of rheumatic origin. This observation shows that restenosis can develop slowly so that some patients will have a relatively long-lasting complaint-free period. As a consequence, we think that on the basis of strict indications percutaneous balloon dilatation of the aortic valve still has a place in relieving aortic stenosis in elderly patients with inoperable severe aortic stenosis.

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1 Cribier A, Savin T, Berland J, Saoudi N, Rocha P, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet* 1986;i:63–7.
2 McKay RG, Safian RD, Lock JE, Diver DJ, Berman AD, Warren SE, Come PC, Baim DS, Mandell VE, Royal HD, Grossman W. Assessment of left ventricular and aortic valve function after aortic balloon valvuloplasty in adult patients with critical aortic stenosis. *Circulation* 1987; 75:192–203.
3 Isner JM, Salem DN, Desnoyers MR, Hougen TJ, MacKey WC, Pandian NG, Eichhorn EJ, Konstam MA, Levine HJ. Treatment of calcific aortic stenosis by balloon valvuloplasty. *Am J Cardiol* 1987;59:313–7.
4 Di Mario C, Beatt KJ, de Feyter PJ, van den Brand M, Essed CE, Serruys PW. Percutaneous aortic balloon dilatation for calcific aortic stenosis in elderly patients: immediate haemodynamic assessment and short term follow up. *Br Heart J* 1987;58:644–52.
5 Safian RD, Berman AD, Diver DJ, McKay LL, Come PC, Riley MF, Warren SE, Cunningham MJ, Wyman RM, Weinstein JS, Grossman W, McKay RG. Balloon aortic valvuloplasty in 170 consecutive patients. *N Engl J Med* 1988;319:125–30.
6 Davidson CJ, Harrison JK, Pieper KS, Harding M, Hermiller JB, Kisslo K, Pierce C, Bashore TM. Determinants of one-year outcome from balloon aortic valvuloplasty. *Am J Cardiol* 1991;68:75–80.
7 Nishimura RA, Holmes DR, Reeder GS, Orszulak TA, Breshnahan JF, Ilstrup DM, Tajak AJ. Doppler evaluation of results of percutaneous aortic balloon valvuloplasty in calcific stenosis. *Circulation* 1988;78:791–9.
8 Geible A, Kasper W, Reifart N, Faber T, Just H. Clinical and Doppler echocardiographic follow-up after percutaneous valvuloplasty for aortic valve stenosis. *Am J Cardiol* 1991;67:616–21.
9 Commeau P, Grollier G, Lamy E, Foucault JP, Durand C, Maffei G, Maiza D, Khayat A, Potier JC. Percutaneous balloon dilatation of calcific aortic valve stenosis: anatomical and haemodynamic evaluation. *Br Heart J* 1988;59:227–38.
10 Safian RD, Mandell VS, Thurer RE, Hutchins GM, Schnitt SJ, Grossman W, McKay RG. Postmortem and intraoperative balloon valvuloplasty in calcific aortic stenosis in elderly patients: mechanisms of successful dilatation. *J Am Coll Cardiol* 1987;9:655–60.
11 Di Mario C, Van Veen LCP, De Baat L, Essed CE, Beatt KJ, Leborgne O, Serruys PW. Computed tomography during experimental balloon dilatation for calcific aortic stenosis. A look into the mechanism of valvuloplasty. *J Interv Cardiol* 1988;1:95–107.
12 Berdoff RL, Strain J, Crandall C, Ghali V, Goldman B. Pathology of aortic valvuloplasty: findings after post mortem successful and failed dilatations. *Am Heart J* 1989;117:688–90.
13 Serruys PW, Di Mario C, Essed CE. Late valve restenosis after successful aortic valvuloplasty. A case report. *Int J Cardiol* 1987;17:210–3.
14 Plante S, Beatt KJ, van den Brand M, Di Mario C, Meier B, Serruys PW. Assessment of the "long sheath" technique for percutaneous aortic balloon valvuloplasty. *Cathet Cardiovasc Diagn* 1990;19:129–35.
15 Serruys PW, Luijten HE, Beatt KJ, Di Mario C, de Feyter P, Essed CE, Roelandt J, van den Brand M. Percutaneous balloon valvuloplasty for calcific aortic stenosis. A treatment "sine cure?" *Eur Heart J* 1988;9:782–94.
16 Silver MD. Obstruction to blood flow related to the aortic valve. In: Silver MD, ed. *Cardiovascular pathology*. London: Churchill Livingstone, 1983:599–619.
17 Farb A, Moses JW, Wallerson DC, Gold JP, Subramanian VA. Valve injury and repair in balloon aortic valvuloplasty. *Cath Cardiovasc Diagn* 1989;18:90–5.

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Failure of balloon dilatation of the pulmonary valve in carcinoid pulmonary stenosis

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Abstract

***Background*—Carcinoid heart disease typically results in pulmonary stenosis and tricuspid incompetence. Percutaneous balloon dilatation is an effective treatment for congenital pulmonary stenosis and has been applied successfully to tricuspid stenosis caused by carcinoid heart disease. The value of balloon dilatation of the pulmonary valve in carcinoid pulmonary stenosis was assessed.**

***Methods*—Two patients with severe congestive heart failure secondary to carcinoid heart disease and with documented pulmonary stenosis had balloon dilatation of the pulmonary valve. In both cases tricuspid regurgitation was also present together with reduced cardiac output.**

***Results*—The procedure was technically successful in both patients. One patient experienced symptomatic benefit for two months and the other experienced no improvement. Both patients subsequently required combined tricuspid and pulmonary valve replacement from which good results and symptomatic improvement were obtained.**

***Conclusion*—Though balloon dilatation of the pulmonary valve is technically feasible it is unlikely to provide useful palliation in carcinoid heart disease. Valve surgery should be considered in patients in whom the malignancy is controlled but carcinoid heart disease is producing drug resistant congestive heart failure.**

Pulmonary and tricuspid valve disease caused by the carcinoid syndrome is a rare cause of congestive heart failure. The usual pattern, of predominantly pulmonary stenosis and tricuspid incompetence, results in a considerable reduction in cardiac output. We describe two patients with carcinoid heart disease who were treated with balloon dilatation of the pulmonary valve.

Case reports

CASE 1

A 51 year old man was referred with a four month history of severe exertional dyspnoea (New York Heart Association grade III) and ankle swelling which had been resistant to diuretic therapy (frusemide 80 mg daily and amiloride 10 mg daily). He had presented four years earlier with diarrhoea, flushing, and palpitation and had been diagnosed as having metastatic carcinoid disease. He had undergone hepatic artery ligation and was receiving subcutaneous α interferon three times a week.

Examination showed a raised jugular venous pressure with a prominent V wave, parasternal lift, ejection murmur in the pulmonary area with a single second sound, ankle oedema, pulsatile hepatomegaly, and ascites. Echo and Doppler cardiography showed severe dilatation of the right side of the heart with tricuspid incompetence and pulmonary stenosis. The instantaneous pulmonary gradient estimated from the Doppler examination was 16 mm Hg.

Cardiac catheterisation showed a stenotic pulmonary valve with a simultaneous peak to peak right ventricular to pulmonary artery gradient of 20 mm Hg, tricuspid incompetence, and a reduced cardiac output as reflected by a pulmonary artery oxygen saturation of 60% (giving a cardiac output of 3·1 l/min calculated by the Fick formula, using assumed oxygen uptake of 117 $ml/min^{-1}m^{-2}$). There was minimal tricuspid stenosis with a gradient (of 2 mm Hg) only during the "a" wave.

Percutaneous balloon dilatation of the pulmonary valve was performed. The valve was easily dilated with two inflations of a 19 mm balloon. No deformity of the balloon was seen during inflation. The gradient was abolished but right ventricular angiography showed persistent thickening and deformity in the region of the valve and there was no change in the pulmonary artery oxygen saturation, suggesting that no immediate improvement in cardiac output had occurred.

The patient experienced no benefit from the procedure and was subsequently referred for surgery without further haemodynamic assessment. At operation the pulmonary valve was found to be stenosed with fibrosed rolled back cusps and the tricuspid valve was stenosed and incompetent with fibrotic leaflets and shortened chordae adherent to the ventricular walls. Pulmonary and tricuspid valve replacement was performed without incident and with resolution of the congestive cardiac failure. The patient's treatment was subsequently changed to octreotide (a somatostatin analogue) and he was well at the time of his last assessment 18 months later.

CASE 2

A 46 year old man was referred with a six month history of severe exertional dyspnoea. He had presented three years previously with abdominal pain and had been diagnosed as suffering from carcinoid syndrome with hepatic metastases. He had been treated

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initially with α interferon and subsequently with octreotide.

On examination he had a raised jugular venous pressure with a prominent V wave, soft pulmonary component of the second heart sound, and ejection murmur in the pulmonary area with a quiet early diastolic murmur at the left sternal edge. Abdominal examination showed tender hepatomegaly.

Echocardiography showed tricuspid incompetence and pulmonary stenosis with incompetence and mild aortic incompetence. Cardiac catheterisation showed a simultaneous peak to peak gradient of 40 mm Hg across the right ventricular outflow tract. There was mild tricuspid stenosis (reflected by an "a" wave gradient of 5 mm Hg), gross tricuspid incompetence on right ventricular angiography, and a cardiac output of 3·2 l/min, calculated by the Fick formula with an assumed oxygen consumption of 118 $ml/min^{-1}m^{-2}$).

Percutaneous dilatation of the pulmonary valve was undertaken with a 20 mm balloon followed by a 23 mm balloon. As in case 1 no nipping of the balloon was observed during inflation. The gradient across the valve was reduced to 15 mm Hg though the angiogram showed persistent thickening and there was no improvement in the pulmonary artery oxygen saturation. The procedure produced immediate symptomatic improvement and the clinical signs of tricuspid regurgitation disappeared.

Unfortunately the improvement was maintained for only two months, when he relapsed. Repeat catheterisation showed recurrence of the pulmonary gradient with a withdrawal gradient of 38 mm Hg and right ventricular pressure of 55/5 mm Hg. In view of these findings and the clinical deterioration he was referred for surgery. At operation the pulmonary valve cusps were heavily thickened and rolled up against the valve ring. The tricuspid valve was grossly disorganised with the posterior cusp heavily thickened and rolled backwards. The tricuspid and pulmonary valves were replaced and he was comparatively well 14 months later.

Discussion

CARCINOID SYNDROME

The carcinoid syndrome is produced by the metabolic products, as yet incompletely identified, of a slowly progressive malignancy usually originating in the small bowel (although occasionally from other sites such as ovary or lung). The syndrome is produced only when the tumour has metastasised to liver, presumably because before this the metabolites are produced in small quantities and are detoxified by the liver. Lesions of the heart valves are reported to occur in about 20% of cases clinically,[1] but if echocardiography is used they are detected in up to 70%.[2 3] There is conflicting evidence about the overall importance of cardiac disease as a cause of death in the carcinoid syndrome: Moertel stated that only 10% of patients with the carcinoid syndrome developed cardiac symptoms and of these half died a cardiac death (about 5% of patients with the syndrome),[1] Thorson *et al* reported that 50% of patients have cardiac failure causing death in 30% of patients,[4] Lundin *et al* that "right ventricular failure is one of the major causes of death in patients with the carcinoid syndrome resulting from midgut tumours,"[5] and Ross and Roberts that "carcinoid heart disease frequently is the cause of death in patients with the carcinoid syndrome".[6] The explanation for this divergence of opinion is not clear, though there may have been differences in the patient populations and, as discussed below, with improved control of the malignancy heart failure may have become an increasingly common problem.

The disease typically affects the right side of the heart: plaques are occasionally found in the left heart but they are rarely of haemodynamic significance.

PATHOLOGY

The anatomical consequences of involvement of the tricuspid and pulmonary valves are narrowing of the valve orifices together with tethering and immobility of the leaflets. Possibly because the two valves are of different sizes this produces principally incompetence with a much lesser degree of stenosis in the tricuspid valve and principally stenosis with a minor degree of incompetence in the pulmonary valve.[6 7] The combination of outflow tract obstruction with atrioventricular valvar incompetence is liable to have a profound effect on cardiac output with the pulmonary stenosis exacerbating the tricuspid regurgitation.

Pathological studies have looked at the distribution and nature of the plaques and there has been speculation about the pathogenesis.[6–9] In a necropsy study of 21 cases the plaques were found to affect the valve structures and also the endocardial surfaces of the right atrium and the right ventricle, though right ventricular plaques were smaller (both in thickness and area). Plaques were also sometimes seen in the great veins and coronary sinus.[6] Histology showed that the atrial and ventricular surfaces of the anterior leaflet of the tricuspid valve were involved in the fibrotic process, but only the ventricular surface of the posterior and septal leaflets of the tricuspid valve and the pulmonary arterial surface of the pulmonary valve.

Ultrastructural studies of the carcinoid plaques have proved interesting.[8 10] It was initially thought that the plaques were of collagen and fibrin but it has been shown by light and electron microscopical studies that they are composed of smooth muscle cells (thought to be derived from primitive mesenchymal cells present normally in the subendocardial layer) in a stroma of acid mucopolysaccharide, collagen, and microfibrils. No elastic fibres are present.[8 10] The lesions are often predominantly superficial and well circumscribed and they were described in the earlier work[8] as being entirely limited to the endocardium and subendocardial layer. However, the more recent study[10] suggested a more infiltrative nature and showed lesions extending into the myocardium.

AETIOLOGY OF PLAQUES

The aetiology of the plaques is unknown. The clinical features of the carcinoid syndrome (flushing, diarrhoea, and bronchospasm), are thought to be produced by the effects of the circulating vasoactive products of the malignancy, including serotonin and its metabolites, tachykinins (neuropeptide K and substance P), prostaglandins, kallikrein and bradykinin.[8 11] There are, however, probably numerous other unidentified compounds at work. It has been postulated that the plaques are a result of the action of these substances on the endocardium and that a resulting increase in endothelial permeability allows migration of primitive mesenchymal cells which then differentiate into the smooth muscle cells seen in the carcinoid lesions. It has been further speculated that this process of endothelial injury is exacerbated by hydrodynamic factors such as turbulence, which might explain the localisation of plaques.[8]

Several studies have attempted to correlate factors such as length of symptoms and concentrations of circulating substances with the presence of heart disease in the carcinoid syndrome. Most have found that the presence of carcinoid heart disease is not associated with a longer duration of symptoms[6 12] but that it is associated with raised concentrations of circulating vasoactive compounds (serotonin-reflected in the urinary concentrations of its metabolite 5-hydroxyindole acetic acid[11 12] and tachykinins[11]), but there have been conflicting findings.[13 14] Though raised concentrations have not been shown to be associated with carcinoid heart disease, bradykinin has also been proposed as an aetiological factor, because it is produced in large amounts, is capable of producing endothelial injury, and its inactivation in the lung might explain the predominance of lesions in the right side of the heart.[8 9]

Evidence also suggests a link between serotonin rich diets and endomyocardial fibrosis in Uganda.[15] Finally methysergide (a serotonin antagonist) can produce retroperitoneal and occasionally valvar and endocardial lesions,[16] both of which point indirectly to the role of serotonin in the aetiology of the plaques.

PROGNOSIS AND THE NEED FOR INTERVENTION

By the time carcinoid heart disease has developed the prognosis is poor with a median survival time of 14 months. In the past most patients died of their malignancy or other complications rather than heart disease.[1] In general, therefore, carcinoid heart disease has been treated conservatively, surgery being reserved for patients thought likely to have an unusually good prognosis. Recently introduced medical treatments have greatly improved the quality of life for many with the carcinoid syndrome. Both α interferon and octreotide (a long acting somatostatin analogue) reduce flushing and diarrhoea in 60–70% of patients, and there is some evidence of improved survival with α interferon.[17 18] If patients survive longer with a better quality of life the relative impact of the cardiac lesions is likely to be greater and it can be expected that the number of patients in good general condition referred for cardiological intervention will increase in the next few years.

We argued that although the pulmonary valve gradients were not great in our two patients, relief of the outflow tract obstruction would reduce the degree of tricuspid regurgitation and improve cardiac output. The dramatic resolution of the tricuspid incompetence in case 2—albeit for only a few weeks—provides some support for this proposition.

Balloon dilatation of the pulmonary valve is a safe technique, with excellent immediate and long-term results in patients with congenital pulmonary valve stenosis. It is the recommended treatment for patients with this condition.[19]

Successful balloon dilatation of carcinoid tricuspid stenosis has been reported in one patient and the authors speculated that balloon dilatation of carcinoid pulmonary stenosis was also likely to be effective.[20] The likely efficacy of balloon dilatation applied to the carcinoid pulmonary valve has also been speculated upon by Cheng.[21] Combined balloon dilatation of the tricuspid and pulmonary valves has also been reported as successful in a patient with combined tricuspid and pulmonary stenosis in the carcinoid heart,[22] not the typical pattern of valve lesions in this disease.

The results in our two patients, however, were disappointing; whereas double valve replacement produced good results. The rapid recurrence of the right ventricular outflow tract obstruction is perhaps not surprising in view of the pathology. Presumably the balloon merely compressed the fibrous plaques, which subsequently recoiled or continued to grow, in contrast to the splitting of fused commissures that is caused by balloon dilatation for pulmonary valve stenosis. The smaller pulmonary valve gradient in case 1 may indicate that in this case the tricuspid regurgitation was a more important cause of congestive cardiac failure than in case 2.

Reported cases of valve surgery for carcinoid heart disease include a series of 13 patients collected from published reports and reviewed by Strickman[9] and a series of 32 reported cases collected more recently by Lundin *et al.*[5] Further cases have also recently been described by Bilinska *et al*[23] and by Fetherston and Davis.[24] Patients undergoing surgery (usually tricuspid valve replacement with either pulmonary valvotomy, valvectomy or valve replacement[5]) have in general done well, with the median survival from Strickman's series being in excess of two years, which is excellent given the natural cause of the disease by the time cardiac symptoms develop.

The two cases described here accord with the view that valve surgery can be expected to produce good symptomatic relief in advanced carcinoid heart disease and is superior to balloon dilatation of the pulmonary valve, which we found to be ineffective.

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1 Moertel CG. Treatment of the carcinoid tumour and the malignant carcinoid syndrome. *J Clin Oncol* 1983;11:727–40.

2 Lundin L, Norheim I, Landelius J, Öberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound detectable cardiac abnormalities. *Circulation* 1988;77:264–9.

3 Lundin L, Landelius J, Andrén B, Öberg K. Transoesophageal echocardiography improves the diagnostic value of cardiac ultrasound in patients with carcinoid heart disease. *Br Heart J* 1990;64:190–4.

4 Thorson A, Biorck G, Bjorkman G, Waldenstrom J. Malignant carcinoid of the small intestine with metastasis to the liver, valvular disease of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects) peripheral vasomotor symptoms, bronchoconstriction and pathologic syndrome. *Am Heart J* 1954;47:796–817.

5 Lundin L, Hansson HE, Landelius, Öberg K. Surgical treatment of carcinoid heart disease. *J Thorac Cardiovasc Surg* 1990;100:552–61.

6 Ross EM, Roberts WC. The carcinoid syndrome: comparison of 21 necropsy subjects with carcinoid heart disease to 15 necropsy subjects without carcinoid heart disease. *Am J Med* 1985;79:339–53.

7 Trell E, Rausing A, Ripa J, Porp A, Waldenstrom J. Carcinoid heart disease; Clinicopathological findings and follow up in 11 cases. *Am J Med* 1973;54:433–44.

8 Ferrans VJ, Roberts WC. The carcinoid endocardial plaque, an ultrastructural study. *Hum Pathol* 1976;7:387–409.

9 Strickman NE, Rossi PA, Massum Kharis GA, *et al.* Carcinoid heart disease. *Current Prob Cardiol* 1982;6:1–41.

10 Lundin L, Funa K, Hansson HE, Wilander E, Öberg K. Histochemical and immunohistochemical morphology of carcinoid heart disease. *Pathol Res Pract* 1991;187:73–7.

11 Lundin L, Norheim I, Landelius J, Öberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation* 1988;77:264–9.

12 Himelman RB, Schiller NB. Clinical and echocardiographic comparison of patients with the carcinoid syndrome with and without carcinoid heart disease. *Am J Cardiol* 1989;63:347–52.

13 Arora RR, Warner RRP. Do indole markers predict carcinoid heart disease. *Chest* 1986;90:87–9.

14 Roberts WC, Sjoerdsma A. The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease). *Am J Med* 1964;36:5–34.

15 McKinney B, Crawford MA. Fibrosis in guinea pig diet produced by plantain diet. *Lancet* 1965;ii:880–5.

16 Graham JR. Methysergide for prevention of headache. Experience in five hundred patients over three years. *N Engl J Med* 1964;270:253–7.

17 Öberg K, Norheim I, Lind E, *et al.* Treatment of malignant carcinoid tumours with human leukocyte interferon. Long-term results. *Cancer Treat Rep* 1986;70:1297–304.

18 Kvols LK, Moertel CG, O'Connoll MS, *et al.* Treatment of malignant carcinoid syndrome, evaluation of a long acting somatostatin analogue. *N Engl J Med* 1986;315:663–6.

19 Fontes VF, Sousa JEMR, Esteves CA, *et al.* Pulmonary valvoplasty—experience of 100 cases. *Int J Cardiol* 1988;21:335–42.

20 Mullins PA, Hall JA, Shapiro LM. Balloon dilatation of tricuspid stenosis caused by carcinoid heart disease. *Br Heart J* 1990;63:249–50.

21 Cheng TO. Nonsurgical treatment of carcinoid heart disease. *Ann Thorac Surg* 1991;51:1046–7.

22 Alcibar VJ, Gochi IR, Onate LA, Inguanzo BR, Alvarez BA, Barreiro GG. Tricuspid and pulmonary percutaneous valvuloplasty in the cardiopathy of the carcinoid syndrome. A case report. *Rev Esp Cardiol* 1991;44:238–7.

23 Bilinska ZT, Miskiewicz Z, Rozanski J, *et al.* Carcinoid heart disease. One-year survival following tricuspid valve replacement and pulmonary valvotomy. *CV World Report* 1990;3:173–8.

24 Fetherston GJ, Davis BB. Surgical management of carcinoid heart disease. *Ann Thorac Surg* 1991;51:493–4.

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Percutaneous balloon dilatation of the mitral valve in patients who were unsuitable for surgical treatment

T R D Shaw, D McAreavey, A R Essop, A D Flapan, A T Elder

Abstract

***Objective*—To assess the effects on haemodynamic function and symptoms of percutaneous balloon dilatation of mitral stenosis in patients unable to undergo surgical treatment because of associated medical/cardiac problems.**

***Design*—A review of clinical outcome in 28 patients (of 108 undergoing balloon dilatation of the mitral valve) who were unsuitable for surgery.**

***Setting*—A tertiary cardiac referral centre: some patients referred were from other cardiac centres in Scotland.**

***Patients*—28 patients judged by cardiac surgeons to be unsuitable for valve replacement or valvotomy because of respiratory disease (15 patients), non-mitral cardiac disease (6), multi-organ impairment (5), psychiatric problems (1) or dense intrathoracic adhesions (1).**

***Interventions*—Percutaneous anterograde balloon dilatation of the mitral valve with polyethylene/polyvinyl balloons in 20 patients and the Inoue balloon in eight patients.**

***Main outcome measures*—Haemodynamic variables were measured before and immediately after mitral valve dilatation. Patient survival and symptom class (New York Heart Association) were followed for a year after the procedure.**

***Results*—Dilatation at the mitral orifice was achieved in all cases. The mean (SD) pressure drop across the valve fell from 13·9 (5·3) to 5·6 (2·5) mm Hg, cardiac output rose from 3·18 (1·02) to 3·96 (2·5) l/min, and valve area increased from 0·78 (0·32) to 1·58 (0·56) cm^2. The procedure was well tolerated by most patients, even those with metabolic/electrolyte disturbance, severe obstructive airways disease, myocardial impairment, and coronary disease. In three patients a small shunt developed at the atrial level: none developed severe mitral reflux. The two patients who required assisted ventilation died soon after the procedure and in one patient with severe coronary artery disease myocardial infarction developed and she died in cardiogenic shock. Early symptomatic improvement was reported by 23 of the 25 survivors, though the increase in exercise capacity was often limited by their non-mitral disease. At one year follow up a further 6 patients had died because of their additional disease: 15 continued to show symptomatic improvement.**

***Conclusions*—Percutaneous balloon dilatation of the mitral valve is a useful new option in patients who are too ill to undergo cardiac surgery; but longer term benefit can be limited by the associated disease.**

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The introduction of percutaneous balloon dilatation created a new option in the treatment of mitral stenosis.[1,2] The place of mitral balloon dilatation in relation to surgical treatment has still to be fully established but balloon dilatation may be useful in patients with additional medical problems that put them at an unacceptably high risk for operation. In Western Europe and North America the proportion of elderly patients with severe mitral stenosis and additional disease is increasing as acute rheumatic fever becomes less common.[3] Also in some patients restenosis develops after a successful surgical valvotomy carried out many years earlier. We report the results of percutaneous balloon dilatation of the mitral valve in patients in whom surgical treatment was regarded as unacceptable.

Patients and methods

PATIENTS

Each patient had been judged by a cardiac surgeon as unacceptable for operation because of medical problems other than mitral valve disease. Patients whom a surgeon was reluctant to accept because of age and or general frailty were not included in this series because these criteria are less clear cut. Nor were the patients who had one or more moderately severe medical problems that would have added to the risk of surgery but did not constitute an absolute contraindication to operation.

There were four groups of principal contraindication to operation:

Group A—Severe chronic obstructive airways disease. There were 15 patients in this group (table 1). They often also had additional problems such as obesity, diabetes, peripheral

Table 1 Clinical characteristics and haemodynamic data before and after balloon dilatation of the mitral valve in 28 patients unsuitable for mitral valve replacement

Patient no	Sex	Age	Rhythm	VTY	NYHA Class (before)	Calcification grade	RV systolic pressure (mm/Hg)		Mean LA pressure (mm/Hg)		Mitral gradient (mm/Hg)		Cardiac output (l/min)		Valve area (cm²)		Left to right shunt	NYHA class (4–8 wk)	NYHA class 1 year
							B	A	B	A	B	A	B	A	B	A			
Group A:																			
1	F	69	AF	0	IV	3	45	NR	35	7	22	7	2·4	2·9	0·46	0·91	0	Died	Died
2	M	77	AF	0	IV	3	42	NR	19	11	10	2	2·8	4·2	0·69	2·23	0	III	Died
3	F	70	AF	0	IV	3	57	NR	16	25	8	12	2·8	3·7	0·65	0·76	0	II	III
4	F	56	AF	0	III	0	55	NR	22	9	15	1	2·3	2·3	0·46	1·89	0	II	II
5	F	55	AF	0	III	1	45	NR	23	17	7	5	3·8	4·6	1·18	1·64	0	II	II
6	F	71	AF	0	IV	2	90	75	24	10	23	4	2·2	3·1	0·34	1·17	0	II	II
7	F	65	AF	+	IV	2	58	35	25	6	13	1	2·3	2·7	0·56	2·30	1·2	III	III
8	M	63	AF	+	IV	3	82	54	24	17	18	7	3·4	3·9	0·75	1·25	0	II	Died
9	M	55	SR	0	III	0	78	52	32	19	25	8	4·4	4·5	0·80	1·40	0	II	II
10	F	75	AF	+	III	3	70	49	27	24	16	5	2·8	3·1	0·58	1·01	1·2	III	III
11	F	53	AF	0	IV	3	105	90	33	22	23	4	1·9	2·5	0·30	1·03	0	I	I
12	F	69	AF	0	IV	2	52	45	29	29	10	9	4·1	4·1	1·14	1·16	0	IV	IV
13	M	71	AF	0	IV	0	37	35	18	16	12	6	5·0	8·5	1·46	3·50	0	II	II
14	F	65	AF	0	IV	3	83	60	28	27	14	5	3·4	3·7	0·68	1·28	0	Died	Died
15	F	71	AF	+	III	0	42	45	21	18	6	4	3·0	3·4	0·90	1·44	0	II	II
Mean (SD)		65·6 (7·7)					70·7 (22·2)	54·0 (17·2)	25·0 (5·6)	17·1 (7·3)	14·8 (6·2)	5·3 (2·9)	3·10 (0·89)	3·81 (1·47)	0·73 (0·32)	1·53 (0·71)			
Group B:																			
16	M	59	AF	0	IV	0	52	NR	28	29	13	6	3·1	3·1	0·78	1·41	0	II	Died
17	M	74	AF	+	III	0	53	NR	19	16	11	6	2·7	4·0	0·77	1·43	0	II	II
18	F	78	AF	0	IV	3	27	32	19	12	3	1	2·8	3·7	1·18	2·02	0	II	II
19	F	75	SR	0	IV	3	153	130	36	29	20	7	3 1	4·6	0·60	1·63	0	III	IV
20	F	74	AF	0	III	2	40	37	22	17	11	6	3·4	5·0	0 84	1·79	1·3	II	II
21	F	74	AF	0	IV	0	45	48	23	29	13	5	3·5	4·0	0·85	1·57	0	III	Died
Mean (SD)		72·3 (6·7)					66·2 (58·3)*	61·7 (45·9)	24·5 (6·5)	22·2 (7·8)	11·8 (5·4)	5·2 (2·1)	3·10 (0·32)	4·06 (0·67)	0·83 (1·19)	1·64 (0·23)			
Group C:																			
22	F	63	AF	0	IV	3	75	NR	22	15	14	7	2·3	3·6	0·60	1 28	0	III	Died
23	M	69	AF	0	IV	0	88	75	41	23	16	5	2·2	3·5	0·56	1·72	0	Died	Died
24	F	58	AF	+	IV	3	60	60	23	23	12	6	1·9	1·9	0·58	0·93	0	III	IV
25	F	72	AF	0	IV	0	65	60	20	22	14	7	4·9	6·0	1·11	1·99	0	III	Died
26	F	60	AF	0	III	0	50	50	29	27	11	6	5·8	5·7	1·62	2·29	0	II	II
Mean (SD)		64·4 (5·9)					65·7 (16·0)*	61·2 (10·3)	27·3 (8·5)	22·1 (4·3)	13·4 (4·3)	6·2 (0·8)	3·42 (1·79)	4·14 (1·70)	0·89 (0·46)	1·64 (0·54)			
Group D:																			
27	F	59	AF	0	III	3	70	60	29	17	14	8	2·2	3·2	0·55	1·65	0	I	I
28	F	70	AF	+	IV	2	65	50	25	20	17	9	4·7	5·6	1·07	1·67	0	III	III
Mean (SD)		64·5 (7·7)					67·5 (3·5)	55·2 (7·1)	27·4 (2·8)	18·5 (2·1)	15·5 (2·1)	8·5 (0·7)	3·45 (1·77)	4·40 (1·69)	0·81 (0·36)	1·66 (0·01)			

SR, sinus rhythm; AF, atrial fibrillation; B, before dilatation; A, after dilatation; LA, left atrial; VTY, previous valvotomy; RV, right ventricular; NR, not recorded.
*Four patients.

and cerebral vascular disease, left ventricular impairment, and coronary artery disease.

Group B—Severe non-mitral cardiac disease: six patients were in this category. Three had severe left ventricular impairment (ejection fractions 10, 15, and 25% and the last two had additional coronary disease) and three had severe diffuse coronary artery disease unsuitable for coronary artery bypass grafts.

Group C—Multiorgan impairment: five patients had severe multi-system medical problems (table 2).

Group D—Miscellaneous: one (patient 27) had severe depression and schizophrenia and one (patient 28), who had previously undergone mitral valvotomy, had dense intrathoracic adhesions that caused an attempt at valve replacement to be abandoned.

The mean (SD) age of the 28 patients was 66·7 (7·4) years (range 53–78). There were 21 women and seven men. A history of rheumatic fever was reported by eight (29%) and seven (25%) had had a valvotomy, including two patients had two previous surgical valvotomies. The mean daily dose of frusemide at the time of dilatation was 144 mg (range 40–500 mg). These 28 patients had been referred from cardiac departments throughout

Table 2 Patients with multi-organ impairment in addition to mitral stenosis

Patient no	Patient diagnosis	Organ impairment				
		Renal	Hepatic	Cerebral	Vascular	Haematological
22	Diabetes mellitus, atherosclerosis/gangrene, low output state	+	+	+	+	+
23	Systemic lupus erythematosus, vasculitis, obstructive airways disease, cerebrovascular disease, left ventricular impairment	+	+	+	+	+
24	Poor left ventricular function, recurrent ventricular tachycardia, persistent electrolyte imbalance, low output state	+	+	+	–	–
25	Dense hemiplegia, low output state, severe tricuspid reflux	+	+	+	–	–
26	Glomerulonephritis, rheumatoid arthritis, anaemia, hypertension, left ventricular impairment	+	–	–	+	+

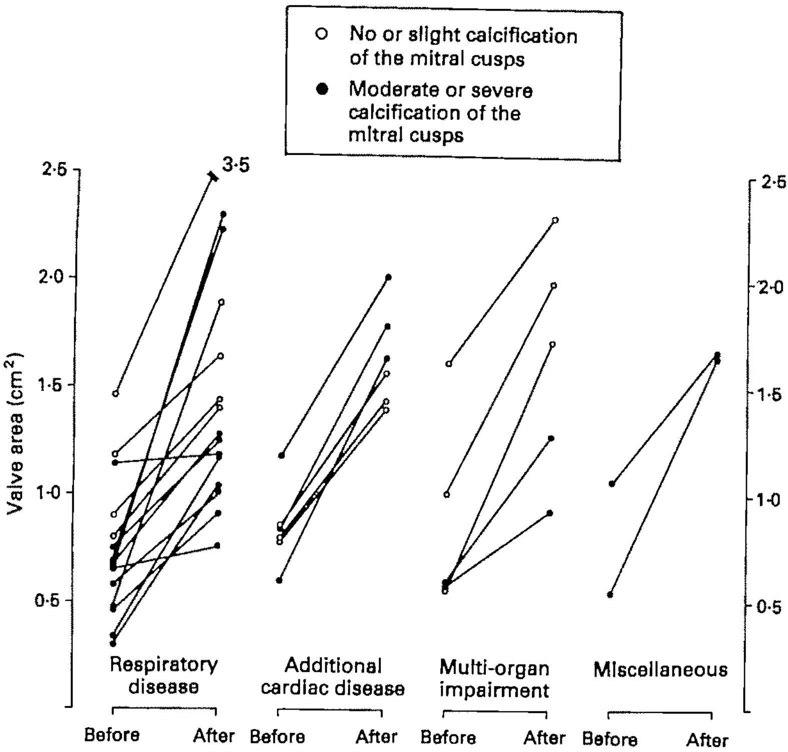

Figure 1 Valve area before and immediately after mitral balloon dilatation: the patients are grouped according to the principal type of contraindication to surgery (see text).

Scotland and they constituted 26% of the patients undergoing balloon dilatation of the mitral valve. Seven of the 28 patients could not leave hospital because of severe symptoms and had urgently required balloon dilatation.

DILATATION TECHNIQUE

The dilatation procedures were carried out in the cardiac laboratory with oxygen and standard resuscitation equipment available. After the procedure the patients were monitored in the coronary care unit.

Patients with respiratory disease were given no premedication but the others were given diazepam (10 mg orally) and, if required, intravenous morphine. One patient (case 1) with severe orthopnoea required a general anaesthetic. Balloon catheters were inserted at the groin under local anaesthesia. The Brockenbrough catheter/needle and the dilatation balloons were advanced to the left atrium from the right femoral vein. An F6 pigtail catheter via the right or left femoral artery was used to monitor aortic pressure and to measure the valve gradient and mitral reflux. An F8 introducer sheath was placed in the left femoral vein to allow access for a pacing electrode and fluid/drug administration if needed. Patients were treated with warfarin for at least four weeks unless anticoagulation was contraindicated and at the time of the procedure all patients were given heparin (100 units/kg body weight).

Table 3 Changes in indices of renal and hepatic function and in cerebral function before and after balloon dilatation of the mitral valve in the five patients with multi-organ impairment

	Blood urea (mmol/l)		*Bilirubin (µmol/l)*		
Patient	*Before*	*After*	*Before*	*After*	*Cerebral function*
22	17·1	6·4	49	42	Improved
23	24·3	15·4	64	74	Worsened (CVA)
24	21·7	6·6	58	35	Improved
25	34·7	16·3	41	34	Improved
26	35·5	35·4	—	—	—

In 20 patients mitral dilatation was carried out with polyethylene (Mansfield Scientific) or polyvinyl/Trefoil (Schneider-Shiley) balloons by the technique described by Lock *et al*[2] except that the guide wire was usually advanced to the left ventricle rather than to the aorta. The Trefoil model (3 × 12 mm) was used for two patients. In the 18 patients treated by polyethylene balloon a single 25 mm balloon was used in 11 and a double balloon technique[4] was used in seven, with sizes from 15 + 15 mm to 15 + 25 mm. The Inoue rubber-nylon balloon technique[5] was used for eight patients, with final dilation sizes of 27 mm (one patient), 28 mm (two patients), 30 mm (three patients), and 32 mm (two patients). All procedures were carried out by one primary operator (TRDS).

Pressures were recorded with zero at 10 cm above the table. Cardiac output was calculated by the Fick principle from oxygen saturations and with an assumed oxygen consumption. After dilatation right heart saturations were measured in the venae cavae to avoid arterial blood from the atrial septal puncture site. The left to right shunt was estimated from right heart oxygen saturations. The mitral valve area was calculated from the modified Gorlin equation:[6 7] diastolic flow/$38 \times \sqrt{\text{mean gradient}}$. Mitral reflux was assessed by the method of Sellars *et al.*[8]

Results

In all patients dilatation at the mitral valve was achieved. Table 1 gives the haemodynamic findings before dilatation and after the final dilatation for each group of patients. Valve area increased in all patients but to a degree that varied from minimal to substantial. For the 28 patients overall, mean (SD) valve area increased from 0·78 (0·32) to 1·58 (0·56) (+103%). In those who had mild or no mitral valve calcification valve area increased from 0·95 (0·35) to 1·84 (0·61) cm², and in those with moderate or heavy calcification it increased from 0·68 (0·25) to 1·41 (0·47) cm² (fig 1). For the 28 patients overall, the valve gradient was reduced from 13·9 (5·3) to 5·6 (2·5) mm Hg (−60%), cardiac output rose from 3·18 (1·02) to 3·96 (1·33) l/min (+25%), and mean left atrial pressure fell from 25·4 (6·0) to 19·1 (6·9) mm Hg (−25%). Right ventricular systolic pressure, measured before and after the procedure in 20 patients fell from 68·5 (28·5) to 57·1 (22·5) mm Hg (−17%). All the changes were statistically significant ($p < 0·001$, paired t test).

Three of the five patients with multi-organ problems who had renal or hepatic impairment showed metabolic improvement within a few days after the procedure (table 3).

The mean duration of the total catheterisation procedure, which included diagnostic catheterisation measurements and coronary

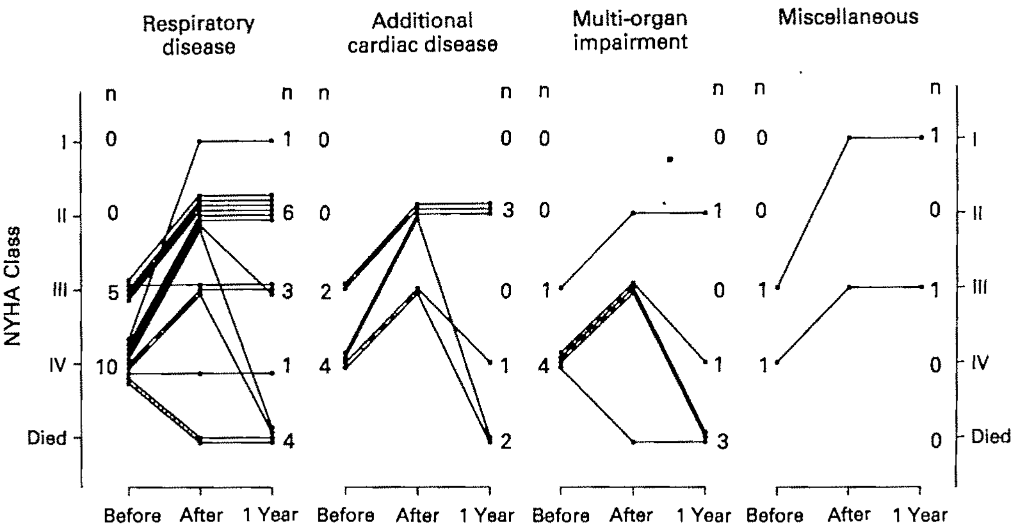

Figure 2 Symptoms before, at 1–2 months after and at one year after balloon dilatation of the mitral valve in patients in groups A–D. NYHA, New York Heart Association symptom class.

angiography in most patients, was 110 minutes (range 60–225). The mean x ray screening time was 36 minutes (range 10–81). The time from beginning to end of each balloon inflation was 5–10 seconds for the polyethylene/polyvinyl balloons and 3–6 seconds for the Inoue balloon. Aortic pressure before, during, and after dilatation was recorded in 23 patients and fell from a mean of 140/71 mm Hg to a mean nadir of 52/39 mm Hg.

Minor complications occurred in four patients. In one (patient 16) brief syncope developed during balloon dilatation. During balloon dilatation one patient (2) with conduction system disease had a period of asystole that responded to a chest thump: a temporary pacemaker was inserted and the procedure was completed. One patient (case 4) required transfusion for blood loss at catheter changes. One patient (case 20) showed an increase of mitral reflux by one grade: she had no reflux before dilatation and showed mild reflux after. A left to right shunt at the atrial crossing point was detected in three patients but was small (1·2, 1·2, and 1·3:1) in each.

There were major complications in three patients. A 69 year old woman (patient 1), with both severe obstructive airways disease (FEV$_1$ 0·4 l) and considerable orthopnoea required a general anaesthetic in order to lie flat for the procedure: she died of respiratory failure six hours later and in retrospect should have been ventilated for longer. Necropsy showed no cardiac complication. A man aged 69 (patient 23) with breathlessness at rest was severely ill with lupus erythematosus and vasculitis which had persisted despite steroid therapy. He also had chronic obstructive airways disease, left ventricular impairment, and a past history of stroke. He became agitated during the procedure and was given intravenous sedation. This caused increased hypoxia and he required assisted ventilation. Evidence of a hemiplegia became apparent two days after the procedure. He died nine days later. He might have benefited from earlier ventilation. The third patient was a 65 year old woman (patient 14) who had obstructive airways disease (FEV$_1$ 0·67 l) with moderately reduced carbon monoxide transfer factor, severe and very diffuse disease of the anterior descending and circumflex coronary arteries, and occlusion of the right coronary artery, considerable pulmonary hypertension, and obesity. The initial arterial oxygen saturation was 83%. Her mitral valve was dilated with the Inoue balloon at 25, 28, and 30 mm sizes. The left ventricular angiogram after the final dilatation showed that left ventricular function, which had been good, had become impaired by appreciable antero-apical hypokinesia. Left ventricular end diastolic pressure had increased from 15 to 25 mm Hg and the ejection fraction had fallen from 71% to 41%. Review of her angiograms showed that a minor apical change had developed after the earlier dilatations. She died of cardiogenic shock three days later and had evidence of anterior infarction. At the final balloon dilatation the systemic blood pressure had fallen from 130/70 to a minimum of 56/48 mm Hg during a four second dilatation period. At necropsy diffuse coronary disease was confirmed but there was no evidence of coronary embolism or thrombosis. A change in left ventricular function was also noted in patient 21 who had severe disease of the circumflex and right coronary arteries. Hypokinesia of the inferior surface developed. Left ventricular diastolic pressure rose from 5–12 to 15–20 mm Hg and the ejection fraction fell from 71% to 36% but acute left heart failure did not develop.

SYMPTOM OUTCOME

Figure 2 and table 1 give the symptom classification of the four groups of patients and compare the symptoms before the procedure with those reported at first follow up 1–2 months later. The improvement in symptoms was limited by the associated non-mitral disease or, in some patients, by a suboptimal haemodynamic result due to considerable degenerative changes in the valve. Twenty three patients improved by one or more symptom classes. In those with respiratory disease 11 of 15 patients reported early improvement, two were unchanged, and two had died. All six patients with additional cardiac disease reported early symptomatic improvement. Four of the five patients with multi-organ medical problems showed some early symptomatic improvement and one had died.

Two patients have had a repeat balloon dilatation procedure for re-stenosis (one five months and one 21 months after the first.)

Twenty one patients were reviewed one year after balloon dilatation and seven were reviewed at 8–12 months (fig 2 and table 1). In the group with respiratory disease two further patients had died: nine (60%) continued to show some symptomatic improvement up to one year after dilatation. Of the six patients with additional severe cardiac disease, two patients had died by one year, two showed continued improvement, and one patient had reverted to NYHA symptom class IV. In the group of five patients with severe general medical problems three had died by one year, one again had breathlessness at rest, and one showed sustained improvement.

Discussion

The patients in this series were all severely disabled by their breathlessness. All had at least one major associated medical problem that put them at an unacceptably high risk as judged by their cardiac surgeon. In these circumstances balloon dilatation of the mitral valve might be considered successful if it produced a small but significant improvement in exercise capacity or prevented clinical deterioration.

In younger patients, most of whom have thin, pliant valves, balloon dilatation has produced excellent results.[2 5 9–13] When the cusps were thickened, immobile, or calcified and there were subvalvar changes in the chordae the haemodynamic improvement was not as good.[14] Abascal *et al* found that when patients had mild degenerative changes in the valves 84% had a "good" result with a final valve area of over 1·5 cm^2 whereas in those with considerable changes 42% had a "good" haemodynamic result and in this group there was a wide scatter of individual results.[15] In our 28 patients who were unsuitable for cardiac surgery symptomatic improvement was often limited by associated disease or by valve calcification or both. However, 12 had a final mitral valve area > 1·5 cm^2 and 21 had a valve area > 1·2 cm^2 with 23 reporting improvement by at least one symptom class at early follow up.

Though it resembles diagnostic cardiac catheterisation, percutaneous balloon dilatation of the mitral balloon takes longer, uses larger balloon catheters, and requires much more manipulation of the catheter and guide wire. It also produces severe hypotension for a few seconds while the inflated balloon obstructs the mitral valve. Nevertheless, most of these severely ill patients tolerated the procedure well. There was, however, some risk in undertaking balloon dilatation in patients with severe associated medical problems. Major, fatal complications related to lung ventilation developed in two patients. Those patients with respiratory problems who could be treated with use of only local anaesthetic and no sedation tolerated the procedure well. Patients with respiratory disease who then require sedation or anaesthesia should have close anaesthetic supervision before and after the procedure and after dilatation should be treated in an intensive care unit rather than a coronary care unit.

Severe mitral reflux developed in 2–4% of patients undergoing balloon dilatation.[10 16] This complication did not develop in our series but it would be a major problem in a patient unable to have emergency mitral valve replacement. This must be considered as a small but significant risk when balloon dilatation is undertaken in patients unacceptable for cardiac surgery. It may therefore be advisable to be cautious with the choice of mitral balloon size. The Inoue balloon, which allows progressively larger dilatations, may help to reduce the incidence of severe mitral reflux. Cerebral embolism and haemopericardium are the two other major but uncommon complications of percutaneous balloon dilatation of the mitral valve.

One patient developed extensive anterior infarction, not due to embolism, after uncomplicated balloon dilatations that had lasted only four seconds. Of our total of 108 patients undergoing balloon dilatation of the mitral valve 22 (20%) had known coronary artery disease and all but one other (patient 21) had tolerated the procedure without overt myocardial impairment. In the light of this complication it seems advisable to restrict the number of inflations and the inflation time in those with critical coronary artery lesions.

The balance of benefit and risk means that balloon dilatation is worth undertaking in patients with severe mitral stenosis who are unsuitable for cardiac surgery. In most patients symptoms will improve. There is some risk attached to the procedure and the improvement in breathlessness may be restricted by the associated disease or because haemodynamic improvement is limited by extensive valve thickening and calcification. Some patients with considerably thickened and calcified valves, however, can obtain good haemodynamic improvement and relief of breathlessness: individual results are unpredictable. For the type of patient included in this series a moderate improvement in symptoms and modest extension of life expectancy can be a sufficient objective to justify attempting balloon dilatation.

1 Inoue K, Owani T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;87:394–402.

2 Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;313:1515–8.

3 Hall RJC, Julian DG. Diseases of the cardiac valves. Edinburgh: Churchill Livingstone, 1989:chapter 1.

4 Palacios I, Block PC, Brandi S, *et al*. Percutaneous balloon valvotomy for patients with severe mitral stenosis. *Circulation* 1987;75:778–84.

5 Chen C, Lo Z, Huang Z, Inoue K, Cheng TO. Percutaneous transseptal balloon mitral valvuloplasty: The Chinese experience in 30 patients. *Am Heart J* 1988;115:937–47.

6 Cohen MV, Gorlin R. Modified orifice equation for the calculation of mitral valve area. *Am Heart J* 1972;84:839.

7 Grossman W. Profiles in valvular heart disease. In: Grossman W, ed. *Cardiac catheterisation and angiography*. Philadelphia: Lea and Febiger, 1985:359–81.

8 Sellars RD, Levy MJ, Amplatz K, Lillelei CW. Left retrograde cardioangiography in acquired heart disease. Technique, indications and interpretation in 700 cases. *Am J Cardiol* 1964;14:437–47.

9 Al Zaibag M, Riberio PA, Al Kasab S, Al Fagih MR. Percutaneous double-balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet* 1986;i:757–61.

10 Vahanian A, Michel PL, Cormier B, *et al.* Results of percutaneous mitral commissurotomy in 200 patients. *Am J Cardiol* 1989;63:847–52.

11 Chen CR, Huang ZD, Lo ZX, Cheng TO. Comparison of single rubber-nylon balloon and double polyethylene balloon valvuloplasty in 94 patients with rheumatic mitral stenosis. *Am Heart J* 1990;119:102–11.

12 Pektas O, Isik E, Coskun M *et al.* Late haemodynamic changes in percutaneous mitral valvuloplasty. *Am Heart J* 1990;119:112–20.

13 Patel J, Vythilingum S, Mitha AS. Balloon dilatation of the mitral valve by a single bifoil (2 × 19 mm) or trefoil (3 × 15 mm) catheter. *Br Heart J* 1990;64:342–6.

14 Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Pecutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;60: 299–308.

15 Abascal VM, Wilkins GT, O'Shea JP, *et al.* Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation* 1990;82: 448–56.

16 Ruiz CE, Allen JW, Lau FYK. Percutaneous double balloon valvotomy for severe mitral stenosis. *Am J Cardiol* 1990;65:473–7.

Br Heart J 1992;67:460–5

Closing sounds and related complaints after heart valve replacement with St Jude Medical, Duromedics Edwards, Björk-Shiley Monostrut, and Carbomedics prostheses

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Abstract

***Objective*—To measure the noise produced and related subjective complaints after implantation of four different mechanical heart valve prostheses and to identify further factors related to the patient and prosthesis that influence noise generation and complaints.**

***Design*—Sound pressure was measured 5 and 10 cm and 1 m from the point of maximal impulse on the body surface by a calibrated meter in quiet rooms with either a decibel(A) filter or octave filters. The patients were asked about their complaints and examined physically.**

***Setting*—The measurements were conducted in silent rooms of ear, nose, and throat departments. The patients had been operated on either in a university hospital or a community hospital.**

***Main outcome measures*—Sound pressures of frequency bands and sound pressures measured in dB(A) at various distances. Complaints registerd were: sleep disturbance, disturbance during daytime, "wants a less noisy prosthesis," and "can hear the closing click".**

***Patients*—143 patients after heart valve replacement with St Jude Medical (n = 35), Duromedics Edwards (n = 38), Carbomedics (n = 34) and Björk-Shiley Monostrut (n = 36) prostheses operated on between 1984 and 1988 were matched for valve position, ring size, and body surface area.**

***Results*—Duromedics Edwards (33·5 (6) dB(A)) and Björk-Shiley Monostrut valves (31 (4) dB(A)) were significantly louder than St Jude Medical (24 (4) dB(A)) and Carbomedics (25 (6) dB(A)) prostheses (p = 0·0001) (mean (SD)). The louder valves were significantly more often heard by the patients (p = 0·0012) and caused more complaints both during sleep (p = 0·024) and during the daytime (p = 0·07). Patients with these valves were more likely to want a less noisy valve (p = 0·0047). Patients with symptoms were younger, had better hearing, and were more likely to be in sinus rhythm. As well as the type of prostheses, the valve diameter and body height also had an effect on sound emission.**

***Conclusions*—The intensity of the closing click of mechanical valve prostheses was significantly different for various designs. Patient complaints were related to the objectively measured sound pressure. Noise production should be considered when a mechanical valve is selected.**

Replacement of stenotic or regurgitant heart valves with mechanical prostheses improves physical ability and long-term survival in patients with congenital or acquired heart valve disease. As well as the risk of complications related to the prosthesis and treatment with anticoagulants—such as embolism, bleeding, and infection—the patients can hear the closing click of the occluders that are typically made from pyrolytic carbon. Complaints about this permanent clicking are generally not noted in the clinical follow up reports. Because the rates of thromboembolic episodes (the complication most affected by valve design) are similar for the currently used mechanical valves, noise generation may well be a criterion for valve selection. We studied the sound intensity produced by various types of mechanical valve prostheses and we investigated whether there is a correlation between the sound emitted and patients' complaints related to noise.

Patients and methods

We studied 143 patients (mean age 57 years (range 26–76)) after valve replacement with St Jude Medical (n = 35), Duromedics Edwards (n = 38), and Carbomedics (n = 34) bi-leaflet valve prostheses and Björk-Shiley Monostrut (n = 36) tilting disk prostheses. All valves have a satisfactory haemodynamic performance[1,2] and a low rate of thromboembolic complications.[3-6] The Duromedics valve had been withdrawn from the market because of reports of mechanical disintegration of the prosthesis with leaflet escape,[7] but was reintroduced after

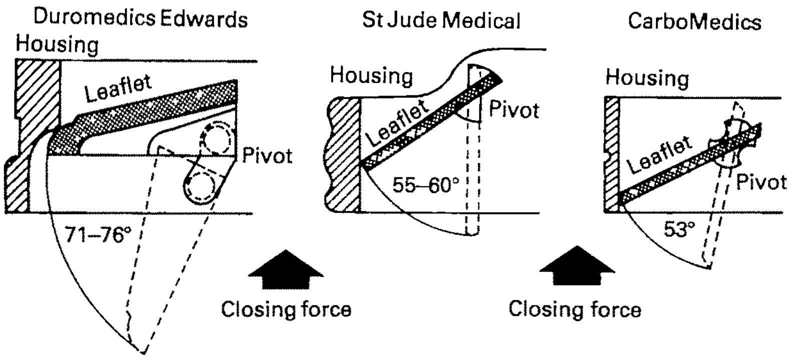


Figure 1 Technical details of the three bi-leaflet valves. The Duromedics Edwards prosthesis has thick, curved leaflets that rotate and move longitudinally in the elongated sockets of the valve housing. The maximal opening angle is 76°. At valve closure the leaflets strike the seating lip of the valve housing. The St Jude Medical valve has a simple pivot articulation and straight leaflets with a maximal opening angle of 85°. The CarboMedics prosthesis also has a simple pivot articulation and its straight leaflets open to 78° maximally. In the closed position the leaflets of both valves rest against the inner aspect of the valve housing at an acute angle.

changes in production methods, the sewing ring, and component tolerances. Though all the bi-leaflet valves are similar in concept there are considerable design differences between them. The St Jude valve has a simple pivot hinge mechanism and its thin, straight leaflets rest against the housing after a maximal rotation of 55°–60°. The leaflets of the Duromedics Edwards valves are curved and move along a combined rotational and longitudinal route in the elongated sockets of the valve housing during valve closure, with a maximal rotation of 71° to 76° (fig 1). The Carbomedics prostheses again has straight leaflets but a smaller maximal opening angle than the St Jude Medical valve. This design feature leads to an earlier onset of valve closure with less regurgitation. The weight of a single leaflet of a 25 mm prostheses is highest for the Duromedics Edwards valve (0·388 g) followed by the St Jude Medical leaflet (0·331 g) and the Carbomedics leaflet (0·28 g). The Shiley Monostrut valve is the most recent version of the Björk prostheses, developed after strut fractures occurred in the convexo-concave valves. At valve closure the occluders of the Björk-Shiley Monostrut and the Duromedics Edwards valves strike a defined structure of the valve housing, a seating lip in the case of the Duromedics Edwards valve and the two struts in the case of the Björk-Shiley Monostrut valve. In St Jude Medical and Carbomedics prostheses the leaflets rest at an angle of 20–26° against the smooth inner aspect of the housing.

Table 1 Patient characteristics (mean (SD))

Valve type	*n*	*Annulus diameter (mm)*	*BSA (m^2)*	*Age (yr)*
		Aortic		
St Jude	21	25·1 (2·3)	1·8 (0·13)	53·5 (11·9)
Duromedics	24	24·4 (2·2)	1·9 (0·15)	56·2 (10)
Björk-Shiley	22	24·3 (2·2)	1·9 (0·2)	58·9 (11)
Carbomedics	22	24·4 (1 6)	1·9 (0·17)	58·9 (11·9)
		Mitral		
St Jude	11	29 (2)	1·7 (0·26)	55 (7·2)
Duoremedics	11	27 5 (0·9)	1·8 (0·15)	55 (13)
Björk-Shiley	11	29 (1·5)	1·7 (0·16)	59·9 (7·5)
Carbomedics	10	27·6 (1·6)	1·7 (0·22)	62·9 (7)
		Aortic and mitral		
St Jude	3	—	1·6 (0·1)	63 (5)
Duromedics	3	—	1·7 (0·15)	56 (7)
Björk-Shiley	3	—	1·8 (0·1)	63 (6)
Carbomedics	2	—	1·7 (0·3)	55

BSA, body surface area.

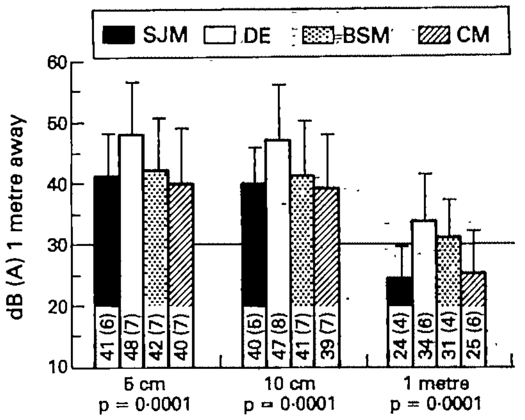
Patients were matched for valve position, tissue annulus diameter, and body surface area (table 1). In the mitral position the valve diameter was smaller for the Duromedics Edwards and Carbomedics valves than for the other groups. Patients completed a questionnaire in which they were asked if they could hear their prosthesis, had their sleep disturbed by the clicking, felt disturbed during the daytime, or would prefer a less noisy prosthesis. The external auditory canal was checked for obstructing foreign bodies. Cardiac rhythm, blood pressure, and the point of maximal impulse of the closing click were determined by physical examination. Sound pressure was recorded with a highly sensitive microphone (Brüel & Kjäer, type 4145, Denmark) over the previously determined point of maximal impulse at a distance of 5, 10, and 100 cm. Sound pressure was measured by a precision sound level meter (Brüel & Kjäer 2204, Denmark) in impulse mode to avoid mean measurements and to ensure the display of peak values. To determine sound pressures according to the frequency dependent hearing level of the human ear we used type A filters, which attenuate low and high frequencies, and recorded measured pressures in decibel(A) (db(A)). The sensitivity for the frequency bands is standardised in IEC 179. The sound level meter was calibrated with a sound level calibrator (Brüel & Kjäer 4230, Denmark). We also used octave filters to measure sound pressure levels (db SPL) for the frequencies 125, 250, and 500 Hz and 1, 2, 4, 8, and 16 kHz. All recordings were done in quiet rooms used for audiometry. The hearing threshold was determined in all patients for frequencies ranging from 125 Hz to 12 kHz for both ears. A Peters audiometer (Sheffield UK) with Telephonics TDH 39 (New York, USA) headphones was used. Patients were asked whether they could still hear the clicking after putting on the headsets. If this was the case broad spectrum noise and band noise was applied through the headsets in increasing intensity to determine the intensity of body conduction.

STATISTICAL ANALYSIS

Statistical comparisons were made on a personal computer with Statview 512 (Brain Power, Calabasas, California) and JMP software. Variables were tested for normal distribution by the F test and were compared by an unpaired t test or χ^2 test. Relations between variables and measured sound pressure were determined by stepwise regression analysis. Further impact of patient and valve related variables on complaints was evaluated by simple and multiple logistic regression analysis.

To compare the hearing threshold and

Figure 2 Comparison of sound pressures measured at different distances. At 5 and 10 cm the Duromedics valve was significantly louder than the other types. At 1 metre the Duromedics Edwards and Björk-Shiley Monostrut valves were louder than the average background noise in a quiet room (30 dB(A)) and the two other valve types. Sound pressures measured at this distance closely resemble those measured next to the patients ear. SJM, St Jude Medical; DE, Duromedics Edwards; BSM, Björk-Shiley Monosrut; CM, CarboMedics.



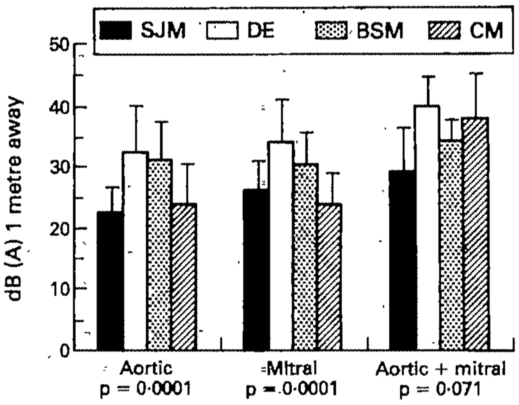


Figure 3 Two implanted prostheses always generated more noise than did one implant. For none of the investigated prostheses was there a significant difference in sound pressures measured at the aortic and mitral positions. See legend to fig 2 for abbreviations.

sound pressure we expressed the hearing threshold in db (SPL) by adding the correction values according to ISO 226 to the respective frequency dependent threshold measured at audiometry.

Results

The sound pressure developed by the prostheses were significantly different at 5, 10, and 100 cm. Five and 10 cm away from the body surface the Duromedics Edwards prostheses were louder than the other valves. At 1 m the Björk-Shiley Monostrut and the Duromedics Edwards valves were significantly louder than the two other valve types and their sound pressure levels were higher than the average level of background noise in a silent room (fig 2). The distance of 1 m seems to be most relevant because the sound pressures measured there are similar to those next to the patient's ear.

Sound pressure for valves in the aortic and mitral positions were similar for all the valve types. After double valve replacement sound pressures were higher than for single valve replacement for all valve types (fig 3). Neither systolic or diastolic blood pressure nor blood pressure amplitude correlated with the measured sound pressure for aortic and mitral prostheses.

The differences in noise generation led to significant differences in sound related complaints. Patients with noisier valves were more likely to have symptoms (table 2) and measured sound pressures were significantly louder in patients with symptoms than in those without (fig 4). The sound pressure levels of the frequency bands were not distributed evenly within the audible range. Low and high frequencies dominated. Differences between symptomatic and symptom free patients were most significant at the higher frequencies (table 3). The human hearing threshold attenuates low and high frequencies so that the audible noise levels between low and middle frequency ranges are equalised (fig 5).

Patients with symptoms had better hearing. Again this difference was most significant in the high frequency ranges (table 4). As a result of higher sound pressures and better hearing the audible noise level was significantly higher for patients with symptoms (fig 6).

To identify factors related to the patient and prostheses that influence the noise developed we entered valve diameter, height, body weight, body surface area, body mass index, rhythm, systolic and diastolic blood pressure into a stepwise regression model. Valve diameter and body height emerged as significant variables. As the size of the prosthesis increased so did the energy released at valve closure and hence the sound pressure levels measured 1 m from the body surface correlated with the tissue annulus diameter of the implanted valve. Body height was an independent variable for developed noise. Body surface area, body weight, or body mass index as an indicator of obesity did not influence developed sound pressure levels nor did blood pressure.

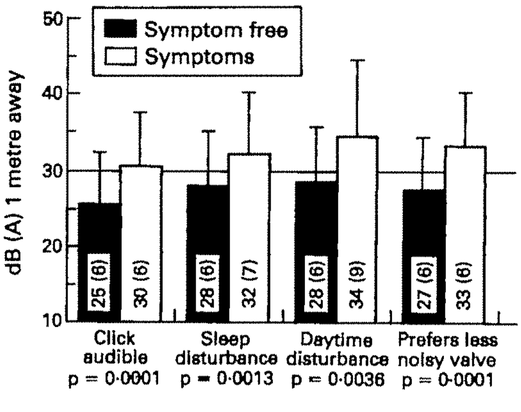


Figure 4 Patients with symptoms had significantly noisier valves. This was true for all four types of complaints.

Table 2 Noise related complaints

Valve type	*Valve audible*	*Sleep disturbance*	*Daytime complaints*	*Prefers less noisy valve*
SJM	22/35 (63%)	3/35 (8·6%)	0/35 (0%)	4/35 (11%)
DE	26/38 (68%)	10/38 (26%)	4/38 (10·5%)	12/38 (32%)
BSM	30/36 (83%)	13/36 (36%)	5/36 (14%)	15/36 (42%)
CM	13/34 (38%)	5/34 (15%)	1/34 (3%)	4/34 (12%)
χ^2	p = 0·0012	p = 0·024	p = 0·07	p = 0·0047

The noisier valve types (Duromedics Edwards (DE) and Bjork-Shiley Monostrut (BSM)) caused significantly more complaints than did the more silent types (St Jude Medical (SJM) and Carbomedics (CM)).

Table 3 Frequency dependent sound pressure levels (dB (SPL)) (mean (SD))

Symptom	*125 Hz*	*500 Hz*	*1 kHz*	*4 kHz*	*8 kHz*	*16 kHz*
Valve audible:						
No	24 (7)	14 (4)	10 (5)*	11 (6)*	20 (8)*	30 (8)**
Yes	25 (5)	15 (3)	12 (3)	13 (4)	24 (7)	34 (7)
Sleep disturbance:						
No	25 (5)	15 (4)	11 (4)	12 (5)	22 (8)*	31 (7)**
Yes	26 (4)	15 (3)	11 (2)	13 (5)	25 (7)	36 (7)
Daytime disturbance:						
No	25 (5)*	15 (4)	11 (4)	12 (5)*	22 (8)*	32 (7)*
Yes	28 (4)	15 (3)	13 (2)	15 (4)	28 (8)	38 (8)*
Prefers less noisy valve:						
No	25 (6)	14 (5)	10 (4)*	12 (5)	21 (8)**	31 (7)**
Yes	26 (5)	15 (3)	12 (3)	13 (5)	26 (7)	37 (7)

*p < 0·05; **p < 0·01.

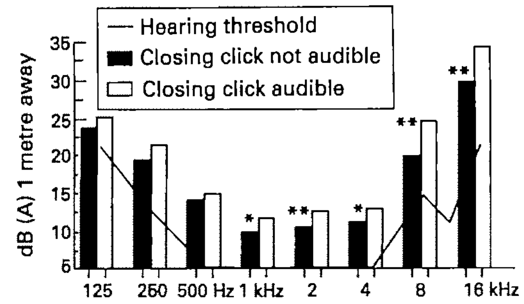


Figure 5 Sound pressure generated by the closing click was higher in the low and high frequency ranges of the audible range, but the effective intensity was attenuated by human hearing characteristics. The high freqency bands of the closing click were perceived most intensely and symptomatic valves produced significantly more noise in these ranges than did asymptomatic ones.

This correlation is true for all patients and for the subgroup after aortic valve replacement (table 5). None of the variables affected the level of developed noise when valves were in the mitral position. A univariate logistic regression analysis showed that sound pressure level (dB(A)), intensity of 8 and 16 kHz frequency sounds, valve type, heart rhythm, hearing level at 8 and 12 kHz, and patient age significantly influenced the occurrence of symptoms (table 6). Sleep disturbances and the request for a less noisy valve were more frequent in patients with intense low frequency body conduction indicated by the level of band noise necessary to override the perception of valve noise. Diastolic blood pressure influenced the audibility of valves only: valve position, body height, body weight, body surface area, and body mass index had no influence on complaints.

All multiple logistic regression models had a value of R^2 of less than 0·29 and thus could not be used to predict the occurrence of symptoms in an individual patient.

Discussion

Though implanted mechanical valve prostheses produce a clicking closing sound that often is audible some distance away from the patient, the relation of this noise level to complaints has rarely been evaluated. For modern prostheses the rates of complications are similar.[3-5 8] So the effect of noise production on the quality of life of the valve carriers should be considered. Our study proved that there is a significant difference in sound emission between the tested prostheses. Differences were more consistent than in vitro results, which were obscured by the noise created by the valve tester.[9]

Noisy valve types clearly caused more complaints, but other variables related to the prostheses and patient also influenced noise production and the rate of complaints. Young patients had hearing in the high frequency range of the closing click (15 to 16 kHz) and thus they perceived the valve noise more intensely than older patients. Patients in sinus rhythm had more complaints than did those in atrial fibrillation, though there was no sigificant difference in measured sound pressure between regular and irregular heart beats. In the logistic regression young age was a much stronger predictor of complaints than sinus rhythm and the higher rate of compaints may thus have been caused by the younger age of patients in sinus rhythm.

The bigger the prosthesis and the greater the occluder mass the higher the energy release at valve closure. The sound pressure increased with annulus diameter. Blood pressure did not influence measured sound pressure nor the rate of complaints, despite its likely influence on the

Table 4 Hearing thresholds (dB(HL)) in symptomatic and asymptomatic patients (mean (SD))

Symptom	*125 Hz*	*500 Hz*	*1 kHz*	*4 kHz*	*8 kHz*	*16 kHz*
Valve audible:						
No	17 (6)	15 (9)	17 (11)*	41 (22)*	49 (23)*	67 (27)*
Yes	17 (8)	12 (8)	13 (10)	28 (19)	33 (23)	54 (28)
Sleep disturbance:						
No	17 (8)	13 (9)	15 (11)	34 (21)*	41 (24)*	60 (28)*
Yes	18 (7)	11 (7)	11(8)	24 (18)	30 (24)	49 (28)
Daytime disturbance:						
No	17 (8)	13 (9)	15 (11)	33 (21)	39 (24)*	59 (28)**
Yes	18 (8)	9 (7)	9 (7)	24 (18)	22 (18)	38 (22)
Prefers less noisy valve						
No	17 (8)	14 (9)*	15 (11)*	35 (21)**	43 (24)**	65 (27)**
Yes	17 (7)	10 (6)	10 (7)	24 (19)	25 (20)	42 (25)

*p < 0·05; **p < 0·01.

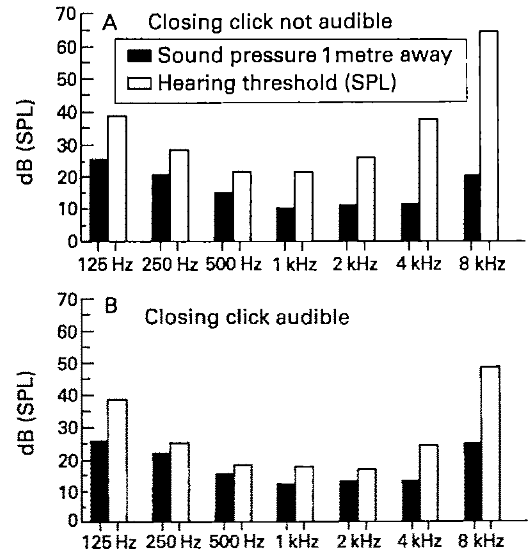


Figure 6 Patients who can hear their valve had louder valves and had better hearing than those who did not. As a result the difference between sound pressure and hearing was significantly greater for the asymptomatic patients (A) than for those with symptoms (B).

Table 5 Variables related to the prosthesis and patient that influenced valve noise determined by stepwise regression analysis of valve diameter and body height on developed sound pressure levels

	Coefficient	*SE*	*Probability*	*Partial F*
All patients:				
Valve size	0·5	0·197	0·01	6·83
Height	0·138	0·054	0·012	6·46
Aortic implants:				
Valve size	0·18	0·085	0·038	4·43
Height	0·74	0·33	0·028	5·03

energy at valve closure. Also in preliminary in vitro studies the relation between blood pressure and sound emission was weak (Wolters H, Theses RWTH Aachen). Not all the variables with an impact on sound generation also influenced the rate of complaints and vice versa.

The closing sound of a mechanical valve prosthesis consists of low frequency oscillations generated by the blood column and tissue structures within the chest and of the high frequency click caused by the vibrations of the occluder.[10] For leaflets made from pyrolytic carbon these high frequencies range between 8 and 16 kHz.[11 12] Sound propagation within the chest is rather complex, because moving blood, air in the lungs, and solid tissues and bones will conduct and reflect sound differently.[13] Because many patients were able to hear their valve when they were wearing headsets, some of the sound must be conducted by the body.

Externally measurable noise increased with body size, but height did not influence the rate of complaints. In obese individuals subcutaneous and interstitial fatty tissue did not dampen sound emisson or reduce complaints. Patients who heard their valve by body conduction had significantly more sleep disturbance. Internally conducted low frequency noise, in the 125 to 250 Hz range, influenced the rate of sleep diturbance and the desire for a less noisy valve.

Greater noise generation may also be related to component wear. The Duromedics Edwards valve was withdrawn from the market after reports about leaflet escape and fractures[7] and the Shiley Monostrut valve is a reinforced version of the 70° convexo-concave Björk valve in which strut fractures and disk embolisations have been reported.[14] Both prostheses were identified as "noisy" valves in our study. Closing energy, calculated from circumferential velocity and leaflet weight, is slightly higher for the St Jude Medical than for the Duromedics Edwards valve.[15] Early valve closure, a smaller travel angle, and lighter leaflets reduce the closing energy of the Carbomedics valve. The monodisc of the Björk-Shiley Monostrut valve strikes the metal strut at the highest circumferential velocity.[15] Small design details seem to cause the differences in noise generation between the three types of bileaflet valves. Compliance of the sewing ring and design of the seating lip are probably more important than the closing energy. This accords with the findings of cavitation bubble formation caused by fluid deceleration at the instant of closure. Increasing the sewing ring compliance and modifications of the seating lip significantly reduced the shock load at valve closure.[16 17]

The noise generated by mechanical valve prostheses causes significant complaints in patients after heart valve replacement. The four modern prostheses that we tested had a similar rate of valve related complications but two noisier types were identified. Because measured sound intensity correlated with the rate of noise-related complaints the generation of sound should be considered when a mechanical valve is selected.

1 Richard GJ, O'Bannon W, More RB. An in vitro comparison of 29 mm mitral Carbomedics and St Jude Medical artificial heart valves. In: Bodnar E, ed. *Surgery for heart valve disease*. London: ICR Publishers, 1990:628–33.
2 Knott E, Reul H, Knoch M. In-vitro comparison of aortic heart valves prostheses. Part 1: Mechanical valves. *J Thorac Cardiovasc Surg* 1988;96:128–33.
3 Thulin LI, Bain WH, Huysmans EH, *et al*. Heart valve replacement with the Björk-Shiley Monostrut valve: early results of a multicenter clinical investigation. *Ann Thorac Surg* 1988;45:164–70.

Table 6 Results of univariate logistic regression analysis of the impact on the occurrence of sound related complaints of various variables related to the patient or prostheses

	All positions			
Variable	*Valve audible*	*Sleep disturbance*	*Daytime complaints*	*Prefers less noisy valve*
Systolic blood pressure	0·44	0·12	0·2	0·7
Diastolic blood pressure	0·014	0·197	0·49	0·21
Blood pressure amplitude	0·026	0·37	0·41	0·78
Body height	0·7	0·21	0·3	0·44
Body weight	0·6	0·97	0·78	0·66
Body surface area	1	1	1	1
Body mass index	0·4	0·064	0·82	0·64
Sinus rhythm/atrial fibrillation	0·011	0·039	0·034	0·0006
Body conduction	—	0·026	0·122	0·1
Sound pressure at 10 cm	0·00032	0·01	0·34	0·0011
Sound pressure at 1 m	0·000003	0·0016	0·0048	0·000004
Sound pressure 125 Hz (1 m)	0·57	0·072	0·025	0·088
Sound pressure 8 kHz (1 m)	0·00034	0·055	0·029	0·0012
Sound pressure 16 kHz (1 m)	0·00022	0·0019	0·021	0·000041
Hearing level 125 Hz	0·98	0·49	0·8	0·89
Hearing level 8 kHz	0·00043	0·025	0·012	0·00019
Hearing level 12 kHz	0·00232	0·057	0·017	0·00011
Age	0·000024	0·019	0·014	0·00015
Band noise 125 Hz	0·75	0·00059	0·13	0·042
Band noise 250 Hz	0·51	0·00161	0·13	0·027
Valve position	0·4	0·47	0·19	0·21
Valve diameter	0·075	0·47	0·22	0·55
Valve type	0·0012	0·024	0·077	0·0047
DE + BSM/SJM + CM	0·0019	0·0047	0·012	0·0005

See footnote to table 2 for abbreviations.

4 Arom KV, Nicoloff DM, Kersten TE, Northrup III WF, Lindsay WG, Emery RW. Ten years' experience with the St Jude Medical valve prostheses. *Ann Thorac Surg* 1989;47:831–7.

5 Geiran O, Froysaker T, Ihlen H, Simonsen S, Vatne K. Carbomedics: a new bileaflet heart valve. In: Bodnar E, ed. *Surgery for heart valve disease*. London: ICR Publishers, 1990:551–7.

6 Klepetko W, Mortiz A, Kühnl-Brady G, *et al*. Implantation of the Duromedics bileaflet cardiac valve prosthesis in 400 patients. *Ann Thorac Surg* 1987;54:14–26.

7 Klepetko W, Moritz A. Leaflet fracture in Duromedics-Edwards bileaflet valves. *J Thorac Cardiovasc Surg* 1989;97:90–4.

8 Moritz A, Klepetko W, Khünl-Brady G, *et al*. Four year follow up of the Duromedics Edwards bileaflet valve prostheses. *J Cardiovasc Surg (Torino)* 1990;31:274–82.

9 Thulin LI, Reul H, Giersiepen M, Olin CL. An in vitro study of prosthetic heart valve sound. *Scand J Thorac Cardiovasc Surg* 1989;23:33–7.

10 Köymen H, Altay BK, Ider YZ. A study of prosthetic heart valve sounds. *IEEE Trans Biomed Eng* 1987;34:853–63.

11 Gordon RF; Najmi M, Kingsley B, Segal BL, Linhart LW. Spectroanalytic evaluation of aortic prosthetic valves. *Chest* 1974;66:44–9.

12 Schöndube F, Keusen H, Messmer BJ. Physical analysis of the Björk Shiley prosthetic valve sound. *J Thorac Cardiovasc Surg* 1983;86:136–41.

13 Meno F, Reddy PS, Bernardi L. Heart sound propagation in the human thorax. *Clin Phys Physiol Meas* 1985;6:123–9.

14 Lindblom D, Rodriguez L, Björk VO. Mechanical failure of the Björk-Shiley valve. *J Thorac Cardiovasc Surg* 1989;97:95–7.

15 Knoch M, Reul H, Rau G. Flow characteristics of six mechanical heart valve prostheses in aortic position: design related model studies In: Bodnar E, ed. *Surgery for heart valve disease*. London: ICR Publishers, 1990:590–601.

16 Kafesjian R, Wieting D, Stobie R. Heart valve sewing ring compliance: The effect on closing impact forces and cavitation bubbles [abstract]. *Int J Artif Organs* 1990;13:607.

17 Wieting DW, Kafesjian R, Stobie R, Adlparvar P, Ward D, Unger J. Hi-speed videography of Edwards-Duromedics heart valve dynamics and fluid dynamics [abstract]. *Int J Artif Organs* 1990;13:608.

Br Heart J 1992;67:466–9

Doppler sonographic evaluation of mechanical and bioprosthetic mitral valve prostheses during exercise with a rate corrected pressure half time

Ph Weiss, A Hoffmann, D Burckhardt

Abstract

***Objective*—To compare the effect of exercise on pressure half time in patients with mechanical or bioprosthetic mitral valves. A relative pressure half time (pressure half time as a percentage of RR interval) was used in an attempt to correct for the shortening of the diastolic time interval caused by the increase in heart rate during exercise and thus to uncover the effects of valve design on pressure half time during exercise.**

***Patients*—Twenty clinically stable (New York Heart Association grade I–II) patients with mechanical (n = 12) or bioprosthetic (n = 8) mitral valves (median age 51) years. The median time since valve replacement was 42 months.**

***Methods*—Continuous wave Doppler echocardiography from the apical view at rest and during moderate supine bicycle exercise (50 W).**

***Results*—During exercise the mean (SD) heart rate increased from 79 (12) to 101 (12) beats per minute (95% confidence interval (95% CI) of difference, 15 to 29/min) and the peak pressure gradient from 11 (5) to 18 (6) mm Hg (95% CI of difference 5 to 9 mm Hg). The pressure half time decreased from 114 (30) to 78 (26) ms (95% CI of difference 30–42 ms). There was no difference between the valve types. The relative pressure half time remained unchanged in patients with mechanical valves during exercise (13 (4) rest and 13 (5)% exercise, respectively) and decreased in patients with bioprostheses (17 (3) and 12 (3)%, respectively (95% CI of difference 2 to 8%, p = 0·025).**

***Conclusions*—In patients with mechanical mitral valves the decrease in the pressure half time during exercise is probably mostly the result of the shortening of the diastolic time interval with increasing heart rate whereas in patients with bioprosthetic valves an increase in functional valve area may contribute to the shortening of pressure half time during exercise.**

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Exercise Doppler echocardiography may be useful in the evaluation of prosthetic mitral valves.[1] In native valves pressure gradients tend to increase and pressure half time tends to decrease during exercise.[2] In patients with mitral valve prostheses the calculation of pressure gradients from flow velocities has been shown to yield reliable results.[3 4] Though the area of the bioprosthetic mitral valve as calculated from the pressure half time at rest did not show a significant correlation with an in vitro model[5] it was useful in distinguishing normal from obstructed mitral bioprostheses.[4 6] In patients with mitral prostheses pressure half time at rest has been shown to be dependent on diastolic filling time but only 19% of the changes of the pressure half time could be explained by this factor.[7] The influence of increasing heart rates during exercise on pressure half time in patients with mechanical or bioprosthetic mitral valves has not been reported yet to our knowledge.

We therefore compared the Doppler sonographic performance of clinically normal mechanical and bioprosthetic mitral valves in exercising patients and corrected the pressure half time for heart rate in an attempt to uncover effects of exercise and valve design on pressure half time.

METHODS

Twelve patients with mechanical mitral valves (five with St Jude Medical prostheses, five with Omnicarbon tilting disc, and two with Starr-Edwards ball prostheses) and eight patients with Ionescu-Shiley mitral bioprostheses were examined. All patients were clinically stable and in New York Heart Association functional class I–II. Patients were studied at rest and during moderate exercise in supine position by a non-imaging continuous wave Doppler transducer from the apical approach (Hewlett-Packard 77070A). Appropriate care was taken to record the maximal velocities and clearest signals possible. The exercise consisted of two minutes at 25 W followed by two minutes at 50 W of supine bicycle exercise. The postion of the Doppler probe was held constant during exercise. Recordings were made at 50 mm/s paper speed at rest and during the last minute of exercise. When the recordings during exercise were not of satisfactory quality we replaced them with those made immediately after exercise (three patients). At least three beats in patients in sinus rhythm (17 patients) and five beats in patients with atrial fibrillation (three patients) were averaged. In all patients peak gradients (by the modified Bernoulli equation) and presure half time were obtained by two investigators by hand.[2] The relative pressure half time ($t\frac{1}{2}$) as percentage of the total RR interval was calculated to correct for changes in heart rate and corresponding shortening of diastole[7 8]:

$$\text{relative } t\tfrac{1}{2} = t\tfrac{1}{2} \times 100/\text{R interval.}$$

M mode echocardiography of the parsternal long axis view at the level of the papillary muscles was used to obtain the end diastolic left ventricular diameter and the shortening fraction.

STATISTICAL ANALYSIS

All values are expressed as mean (SD). Rest and exercise values were compared by the Wilcoxon signed rank test and the two valve types were compared by the Mann-Whitney U test. A p value of $\leqslant 0{\cdot}05$ was regarded as significant (two tailed test). Confidence intervals (95%) were calculated where appropriate.

Results

PATIENTS

Patients with mechanical valves were 30–61 years old (mean 51, median 51 years) and had the valve implanted 12–192 months previously (mean 63, median 42 months). In patients with bioprostheses the respective values were 30–71 years (mean 51, median 50) and 12–153 months (mean 57, median 42). The left ventricular end diastolic diameter was 51 (9) mm (range 36–66 mm) and the shortening fraction was 33 (8)% (range 22–46%) in the patients with mechanical prostheses. In patients with bioprostheses the corresponding values were 48 (11) mm (range 35–65 mm) and 36 (7)% (range 25–46%). There were no significant differences in valve size, patient's age, left ventricular diameter, shortening fraction or time elapsed since implantation of the prosthesis between the two groups. Two patients in each group had mild aortic regurgitation detected by Doppler sonography. Tables 1 and 2 show the values of pressure gradient and pressure half time in patients with mechanical and bioprosthetic valves.

HEART RATE AND PRESSURE GRADIENTS

Two patients with mechanical and one with a bioprosthetic mitral valve were in chronic atrial fibrillation. During exercise the heart rate increased from 75 (9) at rest to 100 (10) beats per minute in patients with mechanical valves and from 84 (13) to 102 (14) beats per minute in patients with bioprostheses (95% CI of difference, 15 to 34 and 5 to 30 respectively). The peak pressure gradient in patients with mechanical valves rose from 9 (2) to 16 (3) mm Hg: in patients with bioprostheses it increased from 14 (8) to 21 (9) mm Hg (95% CI of difference 5 to 8 and 3 to 12 respectively). In both groups the increase in heart rate and peak pressure gradient during exercise was statistically significant ($p \leqslant 0{\cdot}012$).

PRESSURE HALF TIME

In patients with mechanical valves the pressure half time decreased from 106 (26) ms to 80 (25) ms and in patients with bioprostheses it fell from 124 (33) ms to 83 (27) ms (95% CI of difference 13 to 39 and 23 to 79 respectively). In both groups the difference in pressure half time between rest and exercise was significant ($p \leqslant 0{\cdot}012$) but no difference was detected between the groups. However, when the pressure half time was expressed as a percentage of the RR interval (relative pressure half time) to correct for heart rate increase and shortening of the diastolic time interval, patients with mechanical prostheses showed no change in relative pressure half time (13 (4) % at rest and 13 (5)% during exercise) in contrast to the patients with bioprostheses who had a significant ($p = 0{\cdot}025$) decrease from 17 (3)% at

Table 1 Data on patients with mechanical prostheses

Patient	*Type*	*Size (mm)*	*dp rest (mm Hg)*	*dp ex (mm Hg)*	*t½ rest (ms)*	*t½ ex (ms)*	*t½% rest (%)*	*t½% ex (%)*
1	OC	25	12	22	110	90	16	14
2	OC	27	8	12	138	138	17	28
3	OC	29	7	14	71	52	8	9
4	OC	27	11	19	138	55	20	9
5	OC	24	8	15	124	92	17	15
6	SE	30	11	14	86	65	12	10
7	SE	30	7	13	148	115	15	17
8	SJM	29	7	13	92	62	11	11
9	SJM	29	10	21	100	77	11	12
10	SJM	27	9	14	113	85	16	13
11	SJM	27	13	19	79	74	9	14
12	SJM	25	9	18	75	62	9	9

dp, pressure gradient; ex, exercise; OC, Omnicarbon valve; SE, Starr-Edward; SJM, St Jude mechanical; t½, pressure half time; t½%, relative pressure half time as a percentage of RR interval.

Table 2 Data on patients with bioprostheses

Patient	*Type**	*Size (mm)*	*dp rest (mm Hg)*	*dp ex (mm Hg)*	*t½ rest (ms)*	*t½ ex (ms)*	*t½% rest (%)*	*t½% ex (%)*
1	Bio	25	14	21	175	87	18	14
2	Bio	24	7	13	129	62	19	10
3	Bio	25	11	32	130	47	18	9
4	Bio	27	12	14	105	92	15	15
5	Bio	29	8	15	81	67	12	11
6	Bio	25	21	24	157	129	20	16
7	Bio	27	29	36	138	50	19	10
8	Bio	29	9	16	85	59	16	11

*All Ionescu-Shiley bioprostheses. See footnote to table 1 for abbreviations.

Figure 1 Relation between pressure half time and heart rate in patients with mechanical mitral valves at rest and during exercise (paired points for each patient are connected with line).

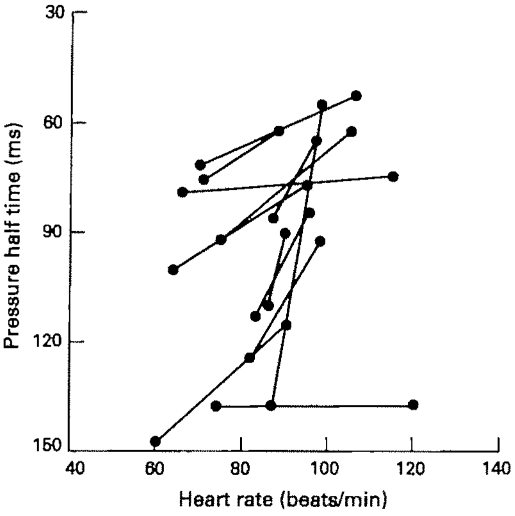
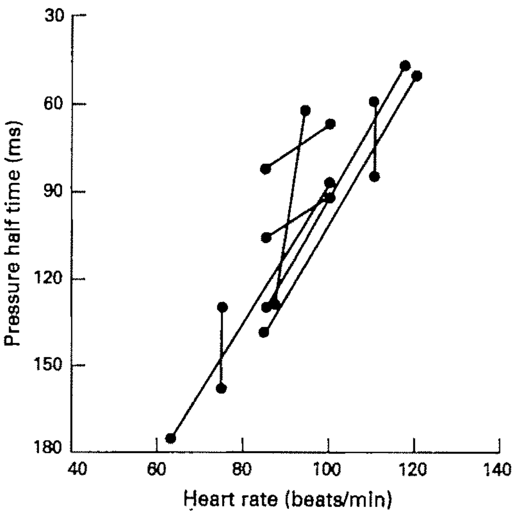


Figure 2 Relation between pressure half time and heart rate in patients with bioprosthetic mitral valves at rest and during exercise (paired points for each patient are connected with line).



rest to 12 (3)% during exercise (95% CI of difference, 2 to 8%). Figure 1 shows the relation between the pressure half time and the rate for mechanical prostheses and fig 2 shows the relation for bioprostheses).

Discussion

Mitral prostheses are slightly stenotic at rest.[9 10] Exercise testing during cardiac catheterisation is commonly used to assess the physiological relevance of stenosis of the native mitral valve. When exercise Doppler echocardiography was used in patients with mechanical mitral valve prostheses a significant increase of peak and mean pressure gradients was seen.[1] However, the behaviour of the pressure half time in mechanical and bioprosthetic valves during exercise has not been compared and the potential influence of the increase of heart rate during exercise has not been taken into account.

INFLUENCE OF EXERCISE ON PRESSURE GRADIENTS

In our patients with bioprosthetic or mechanical mitral valve prostheses moderate exercise significantly increased peak pressure gradients by about 70%. Despite their different designs, during exercise the peak pressure gradients of mechanical and bioprosthetic valves increased to the same extent. This finding accords with the results from Reisner *et al*[1] and resembles the in vitro and in vivo data reviewed by Rashtian *et al.*[9 10]

INFLUENCE OF EXERCISE ON PRESSURE HALF TIME

Cardiac output can influence pressure half time at rest in patients with mechanical mitral prostheses.[7] However, the assumed increase in cardiac output during exercise did not lead to an increase in the calculated mitral valve area in the patients investigated by Reisner *et al*[1] and the relative pressure half time in our patients with mechanical mitral prostheses remained unchanged during exercise. Thus cardiac output may be a factor of minor importance in influencing pressure half time at higher heart rates in patients with prosthetic mitral valves.

Several other factors, such as the loading conditions of the ventricles, compliance of the atria and ventricles, as well as the diastolic time interval influence atrial emptying and thus pressure half time.[7 8 11] Of these only the diastolic time interval is easily measured. A linear relation beteen the RR interval and the diastolic time interval was confirmed recently.[8] We therefore attempted to correct for the decrease in diastolic time interval by calculating a relative pressure half time as a percentage of the RR interval. The analysis of the changes in the pressure half time induced by exercise in our patients showed a significant decrease of about 30% in both groups. However, when the relative pressure half time was calculated a different pattern was found: in patients with mechanical mitral prostheses there were no significant changes during exercise but in patients with bioprostheses there was a significant ($p = 0{\cdot}025$) decrease of 27%. This shows that the pressure half time was shortened more than that of the RR interval during exercise in patients with bioprostheses. The lack of changes in the relative pressure half time during exercise in patients with mechanical mitral valves accords with data generated by cineradiograhic methods and with in vitro data[12–14] which showed an unchanged fully open valve at rest and during exercise in these prostheses. This contrasts with invasive studies based on the Gorlin formula that repeatedly showed an increase in the valve area of mechanical mitral prostheses during exercise.[9] Conversely, high speed photography and video analysis of bioprosthetic valves showed a flow dependent increase of their opening area over a physiological flow range in vitro.[15 16] This increase in functional opening area of mitral bioprostheses with higher flow rates accords well with our finding of a decrease in relative pressure half time during exercise in patients with bioprostheses.

LIMITATIONS OF THE STUDY

Technical aspects

The Doppler echocardiography of patients during or after exercise is technically demanding. Respiration and high heart rates make it difficult to record and interpret. We tried to avoid these problems by using moderate exercise that produced a mean increase in heart rate of 28%. In all our patients the E wave was sufficiently well delineated to allow the analysis of pressure half time during or immediately after exercise in at least 3–5 heart beats. The nature of this study made it difficult to assess inter and intra observer errors without repeating the exercise test on a different day; and variation over time would have added an error of unknown magnitude. However, we believe that the examination of all patients by the same two investigators together will have distributed any methodological variablity equally in both groups and will have enabled us to draw valid conclusions about differences between the groups.

DIASTOLIC TIME INTERVAL AND PRESSURE HALF TIME

Although the pressure half time seems to be related to the diastolic filling period, in a previous study, the relation was weak[7] explaining only 19% of its variablity. In our patients we did not directly measure the diastolic time interval: we replaced it with the RR interval because of the evidence of a linear relation betwen these two variables.[8] Both of these limitations preclude our drawing any firm conclusions about the mechanisms of the different behaviour of the relative pressure half time in the two patient groups. Nevertheless, in bioprostheses, a flow dependent mitral valve area, as seen in vitro, would be a possible and plausible explanation.

CONCLUSIONS

In patients with mechanical or bioprosthetic mitral valve prostheses peak pressure gradients increased considerably during moderate exercise. The pressure half time shortened significantly in both groups, but when the pressure half time was calculated as a percentage of the RR interval only the bioprosthetic valve group showed a decrease. Therefore in patients with mechanical mitral valves most of the decrease of the pressure half time during exercise is probably the result of a shortening of the diastolic time interval with increasing heart rates whereas in patients with bioprosthetic valves a true increase in functional valve area may conribute to the shortening of the pressure half time during exercise.

1 Reisner SA, Lichtenberg GS, Shapiro JR, Schwarz KQ, Meltzer RS. Exercise Doppler echocardiography in patients with mitral prosthetic valves. *Am Heart J* 1989;118:755–9.
2 Hatle L, Angelsen B. *Doppler ultrasound in cardiology: physical principles and clinical applications.* Philadelphia: Lea & Febiger, 1985:119–210.
3 Wilkins GT, Gillam LD, Kritzer GL, *et al.* Validation of continuous-wave Doppler echocardiographic measurements of mitral and tricuspid prosthetic valve gradients: a simultaneous Doppler-catheter study. *Circulation* 1986;74:786–95.
4 Alam M, Rosman HS, Lakier JB, *et al.* Doppler and echocardiographic features of normal and dysfunctioning bioprosthetic valves. *J Am Coll Cardiol* 1987;10:851–8.
5 Dumesnil JG, Honos NH, Lemieux M, Beauchemin J. Validation and applications of mitral prosthetic valvular areas calculated by Doppler echocardiography. *Am J Cardiol* 1990;65:1443–8.
6 Kapur KK, Fan P, Nanda NC, Yopanathan AP, Goyal RG. Doppler color flow mapping in the evaluation of prosthetic mitral and aortic valve function. *J Am Coll Cardiol* 1989;13:1561–71.
7 Chambers J, Jackson G, Jewitt D. Limitations of Doppler ultrasound in the assessment of the function of prosthetic mitral valves. *Br Heart J* 1990;63:189–94.
8 Chambers J, McLoughlin N, Rapson A, Jackson G. Effect of changes in heart rate on pressure half time in normally functioning mitral valve prostheses. *Br Heart J* 1988;60:502–6.
9 Rashtian MY, Stevenson DM, Allen DT, *et al.* Flow characteristics of four commonly used mechanical heart valves. *Am J Cardiol* 1986;58:743–52.
10 Rashtian MY, Stevenson DM, Allen TA, *et al.* Flow characteristics of bioprosthetic heart valves. *Chest* 1990;98:365–75.
11 Thomas JD, Weymann AE. Doppler mitral pressure half time: A clinical tool in search of theoretical justification. *J Am Coll Cardiol* 1987;10:923–9.
12 Verdel G, Heethaar RM, Jambroes G, van der Werf T. Assessment of the opening angle of implanted Björk-Shiley prosthetic valves. *Circulation* 1983;68:355–9.
13 Ishimaru S, Furuawka K, Takahashi M. Cineradiographic evaluation of the convexo-concave Björk-Shiley prosthetic valve in mitral position. *Scand J Thorac Cardiovasc Surg* 1983;17:211–5.
14 Scotten LN, Racca RG, Nugent AH, Walker DK, Brownlee RT. New tilting disc cardiac valve prostheses. *J Thorac Cardiovasc Surg* 1981;82:136–46.
15 Cosgrove DM, Lytle BW, Gill CC, *et al.* In vivo hemodynamic comparison of porcine and pericardial valves. *J Thorac Cardiovasc Surg* 1985;89:358–68.
16 Chambers JB, Cochrane T, Black MM, Jackson G. The Gorlin formula validated against directly observed orifice area in porcine mitral bioprostheses. *J Am Coll Cardiol* 1989;13:348–53.

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Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation

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Andrew N Redington

Abstract

***Objective*—To determine the effects of residual pulmonary regurgitation on exercise tolerance after complete repair of tetralogy of Fallot.**

***Design*—Prospective study of symptom free patients more than five years after complete repair. Graded exercise performance was measured with standard Bruce protocol. Maximal oxygen uptake and ventilatory anaerobic threshold were measured by respiratory mass spectrometry. Measurement of pulmonary regurgitant fraction was from pressure-volume loops constructed from measurements of right ventricular volume obtained from biplane angiograms and simultaneous pressures measured with a micromanometer.**

***Setting*—Tertiary referral centre.**

***Patients*—16 patients were studied. Two patients had been excluded because of residual cardiac lesions or inadequate data from cardiac catheterisation. Four were later excluded because they failed to reach a respiratory quotient of >1·0 during graded exercise.**

***Results*—There was a significant negative correlation between the degree of residual regurgitation and both total duration of exercise and maximal heart rate achieved. Maximal heart rate and total duration of exercise were significantly lower in the patients than in normal controls. Patients with an abnormal maximal oxygen uptake (less than 85% of the predicted normal value) had significantly greater residual pulmonary regurgitation than those in whom oxygen uptake was normal.**

***Conclusions*—Impaired exercise capacity after complete repair of tetralogy of Fallot is directly related to the degree of residual pulmonary regurgitation. These data should be taken into account when deciding the optimal timing and nature of corrective surgery.**

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To achieve complete relief of obstruction of the right ventricular outflow tract after repair of tetralogy of Fallot a pulmonary valvotomy, insertion of an outflow tract patch, or a transannular patch may be required.[1] Consequently, pulmonary regurgitation is present in most patients after corrective surgery, although it is difficult to quantify.

The importance of chronic pulmonary regurgitation in the long term is not established. Previous studies, in which chronic pulmonary regurgitation was assessed qualitatively, suggested that impaired right ventricular function may be related to the degree of pulmonary regurgitation.[2 3] In another study right ventricular volumes were increased and the ejection fraction decreased in patients with a residual ventricular septal defect or pulmonary regurgitation, or both.[4] Several studies have shown impaired exercise ability after complete repair.[5-7] Wessel *et al* found a relation between the degree of impairment of exercise and the heart size on chest radiography, which led them to speculate that residual pulmonary incompetence may be related to exercise ability after operation.[5]

We recently described a new method of measuring the amount of pulmonary regurgitation by analysing right ventricular pressure-volume loops.[8] In our study there was a linear relation between the pulmonary regurgitant volume and right ventricular end diastolic and end systolic volumes. No such relation could be shown, however, between regurgitant volume and the right ventricular ejection fraction.

In the present study we used this technique to examine the possible influence of pulmonary regurgitation on patients' exercise ability after complete repair.

Patients and methods

PATIENTS

The initial study group comprised 18 patients. In two patients data from cardiac catheterisation were unsatisfactory (residual ventricular septal defect (VSD) in one, unsuitable data for analysis in one), and a further four patients failed to achieve a respiratory quotient >1·0 during graded exercise testing (see below). These six patients were not included in the analysis.

Satisfactory data from cardiac catheterisation and exercise were therefore obtained for 12 patients. The table shows the anthropometric data and details of previous surgery for each of the patients. Their median age at the time of corrective surgery was 2·7 (range 0·5–7·7) years with a median follow up of 8·7 (range 5·4–12·7) years. All the patients were well and leading

Demographic, follow up, and exercise data

Patient	*Age (years)*	*Age at operation (years)*	*RVOT gradient (mm Hg)*	*RVEF (%)*	*PR (%)*	*Minutes run*	*Max* Vo_2 *(ml/kg/min)*	*Surgery*
1	14·0	7·7	15	48	27	10	34·2	TAP
2	12·4	2·7	0	60	20	19	55·7	OTP
3	8·7	1·3	10	57	5	15	61·1	TAP
4	14·2	2·7	3	61	0	16·5	55·0	TAP
5	8·4	1·7	47	56	23	14	56·7	TAP
6	13·6	1·7	20	57	58	11	35·5	TAP
7	7·5	0·9	15	47	30	13·5	44·8	PV
8	13·4	3·2	20	48	48	12	45·2	TAP
9	14·4	1·7	18	50	45	11	55·4	TAP
10	8·0	2·8	22	63	50	10	40·8	TAP
11	14·4	5·5	10	64	0	13	44·0	PV
12	10·8	0·5	5	44	39	14	48·0	TAP

RVOT, right ventricular outflow tract; RVEF, right ventricular ejection fraction; PR, pulmonary regurgitant fraction; Vo_2, oxygen uptake; TAP, transannular patch; OTP, outflow tract patch; PV, pulmonary valvotomy.

normal lives with no overt symptoms of reduced exercise tolerance. Cardiac catheterisation and exercise testing were performed according to a protocol agreed by Brompton Hospital's ethical committee, and informed written consent was obtained from the parents of all the patients. Exercise data from the patients were compared with data obtained from 12 controls matched for age, sex, and height.

METHODS

Each patient performed graded maximal exercise, using the progressive treadmill test described by Bruce *et al.*[9] All studies were performed at least one hour after a normal breakfast. A 12 lead electrocardiogram and results of ear oximetry were recorded continuously, and fractional concentrations of all expired gases were measured by respiratory mass spectrometry. Carbon dioxide production, oxygen consumption (Vo_2), and minute ventilation were calculated every 30 seconds with a method described previously.[10] The ventilatory anaerobic threshold was calculated from a plot of minute ventilation against Vo_2.[11] This threshold was defined as the point at which the rate of increase in minute ventilation v Vo_2 diverged from a regression line derived from data points during the first half of the exercise test. All measurements were made until the end of the study. Patients were encouraged to exercise to their limit. Each control underwent a similar protocol. Patients and controls in whom the respiratory quotient at maximal exercise failed to exceed 1·0 were excluded because inadequate effort may have limited their performance.

Cardiac catheterisation was undertaken within 24 hours of the exercise test. All studies were performed under general anaesthesia. Routine haemodynamic measurements were made before angiography. Calibrated biplane right ventriculograms were obtained in 30° right anterior oblique and 60° left anterior oblique projections. Each angiogram was digitised frame by frame throughout a selected cardiac cycle. Extrasystoles, immediate post-extrasystoles, and complexes occurring during the injection of contrast were not analysed. Right ventricular volume was calculated with our multiple slice method.[12] Right ventricular ejection fraction was calculated in the usual way, and peak rates of right ventricular filling and emptying were normalised by dividing by the end diastolic volume.

Simultaneous measurements of intraventricular pressure were taken during ventriculography and recorded at a paper speed of 100 cm/s. The waveform corresponding to the cycle selected from the angiogram was digitised by the same equipment and a pressure-volume loop constructed. The pulmonary regurgitant fraction was calculated from these loops by a method described in detail elsewhere.[8] Briefly, the method allows the pulmonary regurgitation occurring during right ventricular isovolumic relaxation to be measured as the increase in right ventricular volume from the point of end systole until opening of the tricuspid valve (fig 1). This may be expressed as an absolute volume or as a fraction of the total right

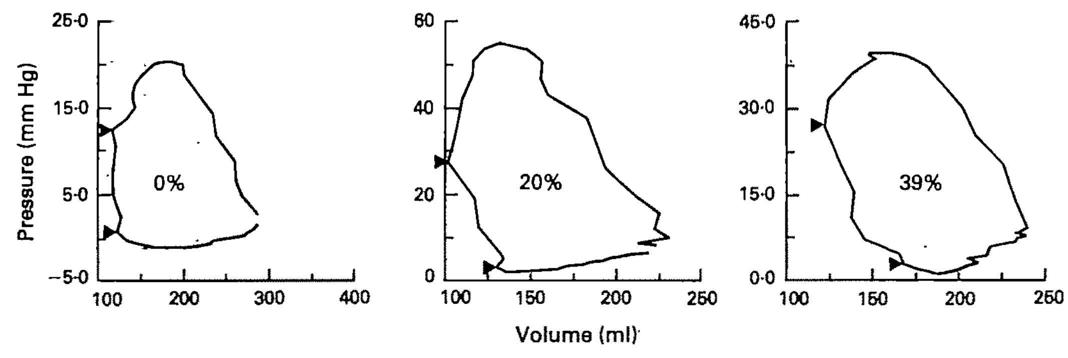

Figure 1 Pressure-volume loops from three of the patients. The amount of pulmonary regurgitation occurring during isovolumic relaxation is measured from the point of minimum cavity volume to the point when the tricuspid valve opens (marked with arrows). The ratio of regurgitant volume to total stroke volume is displayed within the loops and is of increasing severity in these patients.

ventricular stroke volume. Because of concerns about the precision of the calibration process in two of the patients we have chosen to analyse the data only in terms of relative volumes; this does not influence the validity of the data.

STATISTICAL ANALYSIS

Group data were expressed as mean (1 SD). Group data were compared with Student's *t* test or the Mann-Whitney U test. The relations between pulmonary regurgitation and indices of exercise function were examined with a Kendall rank correlation test. The null hypothesis was rejected when $p \leqslant 0{\cdot}05$.

Results

EXERCISE FUNCTION: COMPARISON WITH NORMAL

All patients and controls included in the analysis, developed a respiratory quotient > 1 at maximal exercise. No differences in respiratory quotient, age, height, or body surface area were found between the two groups.

The total duration of exercise was significantly lower in the patients (13·4 (2·7) *v* 18·4 (3·2) min, $p = 0{\cdot}0004$). Maximal heart rate was also lower (180 (17) *v* 197 (6) beats/min, $p < 0{\cdot}01$), as was maximal oxygen uptake (48 (8·8) *v* 52 (7·1) ml/kg/min), although this failed to reach significance. Five patients but only one control failed to reach 85% of the predicted value for maximal Vo_2, suggesting an abnormal response in these subjects.[11] Ventilatory anaerobic threshold tended to be lower in the patients (36·9 (4·6) *v* 39·5 (4·7) ml oxygen kg/min), but this difference also failed to reach significance.

PRESSURE-VOLUME RELATION

None of the patients included in the analysis had appreciable tricuspid regurgitation or residual ventricular septal defect.

The right ventricular end diastolic pressure ranged from 2 to 13 mm Hg (median 6 mm Hg), and only one patient had a pressure gradient across the right ventricular outflow tract of more than 22 mm Hg (table). Analysis of the pressure-volume loops showed that the right ventricular ejection fraction ranged from 44% to 63% (median 57%). Considerable pulmonary regurgitation was present in all but two of the patients, ranging from 0% to 58% of the total stroke volume. There was a significant relation between the degree of pulmonary regurgitation and the gradient across the outflow tract ($r = 0{\cdot}49$, $p = 0{\cdot}025$), reflecting this increased stroke volume. There was no significant relation between the pulmonary regurgitant fraction and right ventricular end diastolic pressure, ejection fraction, or normalised peak rate of ventricular filling or emptying.

EXERCISE FUNCTION AND PULMONARY REGURGITATION

There was a significant relation between the degree of pulmonary regurgitation and both duration of exercise ($r = -0{\cdot}43$, $p < 0{\cdot}05$) and maximum heart rate ($r = -0{\cdot}46$, $p < 0{\cdot}05$). A similar relation was found between the pressure gradient across the right ventricular outflow tract and total duration of exercise ($r = -0{\cdot}55$, $p = 0{\cdot}012$), which almost certainly reflected the relation between pulmonary regurgitation and gradient (see above) rather than being directly linked to the modest residual obstruction in most of the patients.

There was no significant relation between the regurgitant fraction and either maximal oxygen uptake or ventilatory anaerobic threshold. Figure 2 shows that in the five patients in whom the Vo_2 was less than 85% of the predicted normal value the pulmonary regurgitant fraction was significantly higher than that in the remainder of the group (43 (13) *v* 19 (18), $p < 0{\cdot}03$).

Discussion

This study shows a clear relation between the degree of residual pulmonary regurgitation and reduced exercise tolerance in patients after complete repair of tetralogy of Fallot.

Our data confirm the findings of previous studies and show that, when compared with normal subjects, these patients have a reduced maximal exercise tolerance.[5–7] The reason for this has, to date, remained unclear. Right ventricular enlargement and a reduced ejection fraction have been shown in several studies[3,4] but these variables in themselves do not seem to be related to exercise ability. The link between exercise ability and pulmonary regurgitation has not previously been examined in detail. This is because of the difficulty in measuring accurately the amount of regurgitation present in individual patients.

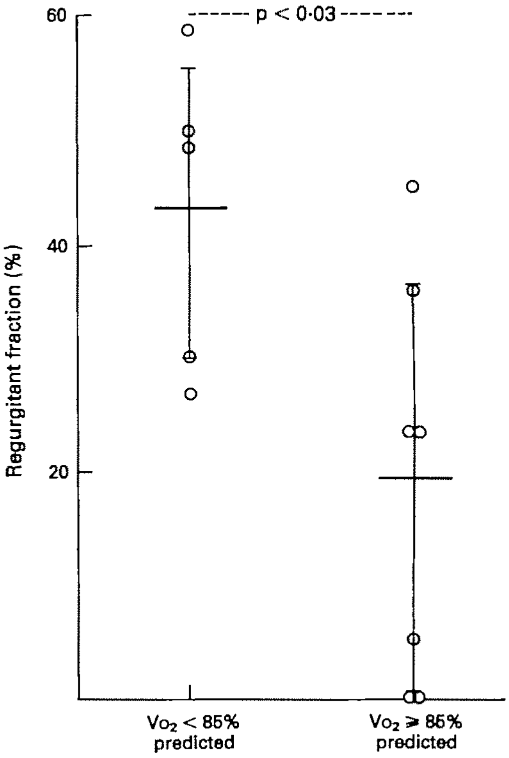

Figure 2 Scattergram showing the relation between pulmonary regurgitant fraction and maximum oxygen uptake (Vo_2).

We recently described a new method of assessing pulmonary regurgitation from analysing right ventricular pressure-volume loops.[8] Our data showed that increased right ventricular volumes, but not ejection fraction, were linearly related to the degree of residual regurgitation. Wessel *et al*'s data are interesting in this regard.[5] They showed that reduced exercise capacity in patients after operation could be related to the heart size measured from the chest radiograph. They speculated that this may in turn reflect the degree of pulmonary regurgitation present and suggested a possible link between residual pulmonary regurgitation and intolerance to exercise in these patients. Our results confirm that this is indeed the case. Pulmonary regurgitation had a deleterious effect on exercise capacity in our patients, whom we studied at least five years after complete correction. The reduction in total duration of exercise and maximum heart rate were both directly related to the degree of regurgitation. In the subgroup of patients with an abnormal maximal oxygen uptake, pulmonary regurgitation was significantly greater than that in the patients in whom maximal oxygen uptake was normal.[11]

These results have obvious clinical implications. Residual pulmonary regurgitation is clearly undesirable, and efforts to reduce it may benefit patients, exercise ability in the long-term after complete repair. Whereas our data suggest a similar relation between residual obstruction of the right ventricular outflow tract and exercise capacity, the residual gradient was less than 25 mm Hg in 11 of the 12 patients. These modest gradients are almost certainly directly related to the degree of pulmonary regurgitation with its consequent increase in stroke volume rather than representing haemodynamically important obstruction. Indeed, there was no relation between more severe obstruction and exercise ability in the patients studied by Wessel *et al*.[5]

These data may influence surgical decision making. Some residual obstruction of the right ventricular outflow tract may be more desirable than complete relief of obstruction at the expense of increased pulmonary regurgitation. The potentially harmful effects of a high right ventricular to left ventricular pressure ratio soon after operation cannot, however, be ignored.[13] An alternative approach is to place a homograft monocusp in the right ventricular outflow tract. Although this technique probably reduces early regurgitation, the function of these valves in the longer term is unknown. Our department is currently investigating this.

Frequently a transannular patch will be required to ensure adequate relief of obstruction of the right ventricular outflow tract in patients with tetralogy of Fallot. If a monocusp valve is not inserted there may well be free pulmonary regurgitation. This must be taken into account when considering the trend towards earlier, usually primary, complete repair during infancy. The frequency of applying transannular patches is undoubtedly higher in young infants[14] and though there may be theoretical advantages to earlier surgery, the documented adverse effects of chronic pulmonary regurgitation on both exercise performance and the incidence of late arrythmias cannot be disregarded.[3] Although we followed up our patients for five to 12 years after operation, the potential effects of chronic pulmonary regurgitation in the longer term need to be examined. These patients will require careful extended follow up.

In summary, we have shown a direct relation between the degree of pulmonary regurgitation and impaired exercise ability in patients after repair of tetralogy of Fallot. This must be taken into account when deciding the optimal timing and nature of corrective surgery.

We thank Dr J Bowyer for providing the control data and the members of the Brompton Hospital lung function unit for their help with the exercise studies.

1 Pacifico AD, Bargeron IM, Kirklin JW. Primary correction of tetralogy of Fallot in children less than four years of age. *Circulation* 1973;48:85–91.
2 Bove EL, Byrum CJ, Thomas FD, Kavey RW, Sondheimer HM, Blackman MS, *et al*. The influence of pulmonary insufficiency on ventricular function following repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 1983; 85:691–6.
3 Zakha KG, Horneffer PJ, Rowe SA, Neill CA, Manolio TA, Kidd L, *et al*. Long-term valvular function after total repair of tetralogy of Fallot. Relation to ventricular arrhythmias. *Circulation* 1988;78:III 14–9.
4 Lange PE, Onnasch DGW, Bernhard A, Heintzen PH. Left and right ventricular adaptation to right ventricular overload before and after surgical repair of tetralogy of Fallot. *Am J Cardiol* 1982;50:786–94.
5 Wessel HU, Cunningham WJ, Paul MH, Bastanier CK, Muster AJ, Idriss FS. Exercise performance in tetralogy of Fallot after intracardiac repair. *J Thorac Cardiovasc Surg* 1980;80:582–93.
6 Hirschfield S, Tuboku-Metzger AJ, Borkat G, Ankeney J, Clayman J, Leibmaniebman J. Comparison of exercise and catheterisation results following total surgical correction of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 1978;75:446–54.
7 Srtreider DJ, Aziz KU, Zaver AG, Fellows KE. Exercise tolerance after repair of tetralogy of Fallot. *Ann Thorac Surg* 1975;19:397–406.
8 Redington AN, Oldershaw PJ, Shinebourne EA, Rigby ML. A new technique for measuring pulmonary regurgitation: application to the assessment of right ventricular function before and after repair of tetralogy of Fallot. *Br Heart J* 1988;60:57–65.
9 Bruce RA, Kasumi F, Hosmer D. Maximal oxygen uptake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85: 546–62.
10 Bowyer JJ, Busst CM, Till JA, Lincoln C, Shinebourne EA. Exercise ability after Mustrards's operation. *Arch Dis Child* 1990;65:865–70.
11 Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis* 1975;112:219–49.
12 Redington AN, Gray HH, Hodson ME, Rigby ML, Oldershaw PJ. Characterisation of the right ventricular pressure-volume relationship using angiography and simultaneous micromanometer pressure measurements. *Br Heart J* 1988;58:23–30.
13 Kirklin JW, Blackstone EH, Pacifico AD, Kirklin JK, Bargeromn IM. Risk factors for early and late failure after repair of tetralogy of Fallot, and their neutralization. *Thorac Cardiovasc Surg* 1984;32:208–14.
14 Tougti GD, Vouhe PR, Amodeo A, Pouard P, Mauriat P, Leca F, *et al*. Primary repair of tetralogy of Fallot in infancy. *J Thorac Cardiovasc Surg* 1990;99:396–403.

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Effects of vasoactive neuropeptides on human saphenous vein

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Abstract

***Objective*—To assess the role of neuropeptides in the control of vascular tone in the human saphenous vein the actions of substance P, vasoactive intestinal peptide, calcitonin gene related peptide, neuropeptide Y, and somatostatin on this blood vessel were examined.**

***Methods*—In vitro organ bath techniques were used with preparations of saphenous veins obtained from 29 patients (aged 41–66) who were undergoing coronary bypass surgery.**

***Results*—Substance P, vasoactive intestinal peptide, and calcitonin gene related peptide relaxed pre-constricted vessels in a dose dependent manner with a rapid onset of action, taking one to two minutes to reach a plateau at each dose. Substance P (10^{-9} to 10^{-6} mol/l) induced relaxation with a maximum response (mean (SEM)) 23·0 (6·6)% of the total relaxation induced by glyceryl trinitrate 1 μg/ml and a 50% maximal effective concentration of 6·8 × 10^{-9} mol/l. Vasoactive intestinal peptide (10^{-10} to 10^{-7} mol/l) produced a relaxation of 27·0 (5·1)% at 10^{-7} mol/l. The maximum responses induced by substance P and vasoactive intestinal peptide were significantly reduced, to 3·7 (2·8)% and 4·7 (2·0)% respectively, after removal of the endothelium. Calcitonin gene related peptide (10^{-10} to 10^{-7} mol/l) elicited only 14·3 (2·6)% relaxation at 10^{-7} mol/l, and this was not affected by removal of the endothelium. By contrast, neuropeptide Y and somatostatin exerted concentration dependent constriction on resting vessels. Neuropeptide Y (10^{-10} to 10^{-7} mol/l) caused prolonged contraction (roughly 20 minutes to reach a maximum plateau at each dose). At 10^{-7} mol/l, the constriction amounted to 28·0 (12·0)% of the response to 90 mM KCl, in ring segments with or without endothelium. Somatostatin (10^{-10} to 10^{-6} mol/l) quickly caused contraction with a maximum response of 42·7 (15·0)% and a 50% maximal effective concentration of 6·7 × 10^{-6} mol/l. The constriction was greatly increased when endothelium was removed, with a maximum response of 78·2 (16·8)% and a 50% maximal effective concentration of 4·3 × 10^{-7} mol/l.**

***Conclusions*—Vasoactive peptides have diverse effects on the vascular tone of the human saphenous vein. Some of these effects are endothelium dependent. The exact physiological role and implication for performance of bypass grafts require further investigation.**

The control of vascular smooth muscle tone may partly be mediated by peptidergic mechanisms. Neuropeptides are ubiquitously distributed in human blood vessels,[1] contributing to vasodilatation (through endothelium dependent or direct action on smooth muscle) and vasoconstriction.[2 3] The endothelium has an important role in controlling vascular tone through the secretion of relaxing and contracting factors derived from the endothelium.[4–6] Several peptides induce significant vasomotor effects in human blood vessels through endothelium dependent and endothelium independent mechanisms.[3 7 8]

The human saphenous vein is of particular interest as it is the vessel most commonly used for aortocoronary artery bypass grafting.[9] Understanding the mechanisms that control vascular tone in this vessel will help the understanding of how the saphenous vein behaves as a bypass graft. We therefore examined the effects of five endogenously occurring peptides on isolated human saphenous veins.

Methods

The study was performed on 111 ring segments taken from 29 patients (aged 41–66) undergoing coronary artery bypass surgery. Human saphenous veins were placed immediately in modified Tyrode's solution composed of 136·8 mM NaCl, 11·9 mM $NaHCO_3$, 2·6 mM KCl, 0·4 mM NaH_2PO_4, 2·5 mM $MgCl_2$, 2·5 mM $CaCl_2$, 11·1 mM glucose, and 0·04 mM disodium EDTA. The veins were dissected free of adherent tissues and cut into ring segments 3–5 mm long, which were mounted on two L shaped metal hooks in 5 ml organ baths within one hour. The organ bath solution was maintained at 37°C and gassed continuously with a mixture of 95% oxygen and 5% carbon dioxide. One hook was fixed and the other attached to a force displacement transducer (Grass FTO-3C). The transducer was connected to a polygraph (Grass 79D) which monitored isometric changes in the tension of the vessel wall.

After an initial pre-tension of 60 mN was applied to each vessel the segments were allowed to relax out to a stable baseline. They

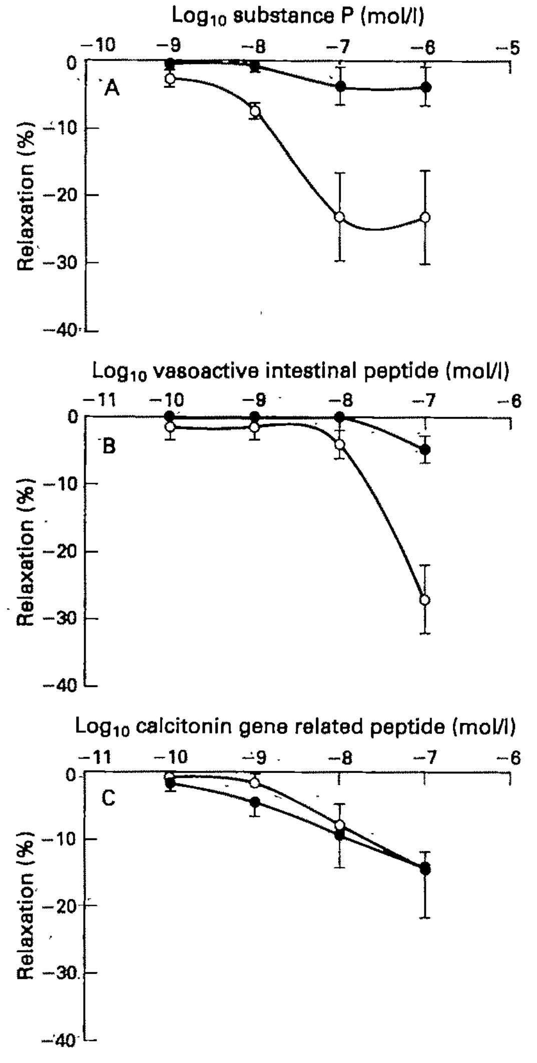

Figure 1 Relaxant effect (measured as percentage of that induced by glyceryl trinitrate 1 µg/ml) of increasing doses of substance P (A, n=7), vasoactive intestinal peptide (B, n=4), and calcitonin gene related peptide (C, n=6) on the human saphenous vein in the presence (○) and absence (●) of endothelium.

were then challenged twice with 90 mM KCl to assess the viability of each vessel segment. When the maximum response to each dose of KCl had been measured the buffer solution was changed twice and the vessels allowed to return to their resting tension.

Dose-response curves were determined for several different peptides. Each peptide was added to the bath cumulatively in log$_{10}$ units until the maximum response of each vessel to each dose of drug had been reached. Each segment was tested with only a single peptide. Some ring segments were pre-constricted with the thromboxane mimetic U46619 to achieve a tension of 60–70% of the contraction seen with KCl before peptides were added.

To assess the endothelium dependent action of peptides some vessel segments were denuded by gently rubbing the intimal surface with a metal spatula. These segments showed absence of endothelium when examined histologically with the specific endothelium marker EN4.

All drugs used (substance P, calcitonin gene related peptide, neuropeptide Y, and somatostatin (Sigma) and vasoactive intestinal peptide (Peninsula)) were reconstituted in distilled water and stored at −20°C. Aliquots were diluted in modified Tyrode's solution immediately before use.

The contractile effect was expressed as the percentage of the maximum contraction induced by 90 mM KCl, and the relaxation response was calculated as the percentage of the response induced by glyceryl trinitrate (1 µg/ml. Data are given as means (SEM). In all experiments n is the number of patients from whom the blood vessels were taken and at least six segments were taken from each patient. The unpaired Student's *t* test was used for statistical analysis, and $p < 0.05$ indicates a statistical difference.

Results

Initial studies showed that cumulative addition of substance P, vasoactive intestinal peptide, and calcitonin gene related peptide had no effect on resting vessels. Pre-constricted segments, however, relaxed to these peptides in a dose dependent manner, with a rank order of maximum relaxation: substance P = vasoactive intestinal peptide > calcitonin gene related peptide. They all quickly induced relaxation, which lasted 1–2 minutes for each dose. Substance P (10^{-9} to 10^{-6} mol/l) produced relaxation with a maximum response of 23·0 (6·6)% and a 50% maximal effective concentration of 6·8 × 10^{-9} mol/l (fig 1A). Vasoactive intestinal peptide (10^{-10} to 10^{-7} mol/l) induced relaxation up to 27·0 (5·1)% at the highest dose used (fig 1B). The maximal vasodilatations achieved by substance P and vasoactive intestinal peptide were significantly attenuated to 3·7 (2·8)% and 4·7 (2·0)% respectively after removal of the endothelium ($p < 0.01$). Calcitonin gene related peptide (10^{-10} to 10^{-7} mol/l) caused only 14·3 (2·6)% relaxation at 10^{-7} mol/l, and this was not affected by removal of endothelium (fig 1C).

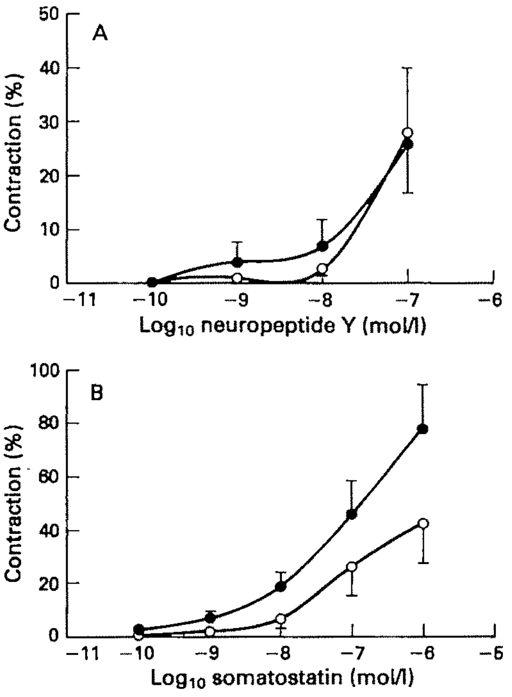

Figure 2 Contractile effect (measured as percentage of maximum concentration induced by 90 mM KCl) of neuropeptide Y (A, n=6) and somatostatin (B, n=6) on the human saphenous vein in the presence (○) and absence (●) of endothelium.

Glyceryl trinitrate (1 μg/ml) relaxed pre-constricted blood vessels back to their resting tension but no further. This suggests that glyceryl trinitrate does not reduce resting tension.

Neuropeptide Y and somatostatin caused further constriction of pre-constricted vessels. Cumulative administration of these peptides resulted in contraction of resting vessels that depended on the concentration. Neuropeptide Y (10^{-10} to 10^{-7} mol/l) induced prolonged contraction (roughly 20 minutes for each dose to reach its maximum plateau), amounting to 28·0 (12·0)% at 10^{-7} mol/l, and this effect was unaltered by removing the endothelium (fig 2A). Somatostatin (10^{-10} to 10^{-6} mol/l) quickly elicited contraction, each dose taking roughly two minutes to reach its maximum effect. Somatostatin had a maximum response of 42·6 (15)% and a 50% maximal effective concentration of $6 \cdot 7 \times 10^{-6}$ mol/l. This constriction was significantly increased when the endothelium was removed, the response being 78·2 (16·8)% and the 50% maximal effective concentration $4 \cdot 3 \times 10^{-7}$ mol/l ($p < 0 \cdot 01$; fig 2B).

Discussion

Peptidergic mechanisms have been implicated in controlling vascular smooth muscle tone.[10 11] The neuropeptides used in our study (substance P, vasoactive intestinal peptide, calcitonin gene related peptide, neuropeptide Y, and somatostatin) are widely distributed in the body and have vasoactive effects on several human vascular beds.[3 12 13] We have shown that substance P, vasoactive intestinal peptide, and calcitonin gene related peptide are weak vasodilators whereas neuropeptide Y and somatostatin elicit constriction in human saphenous vein.[5]

The mode of action of substance P has been studied in the human coronary and gastroepiploic arteries.[14 15] It induces vasodilatation by interacting with the endothelium to release nitric oxide, which has recently been identified as the substance responsible for the action of endothelium derived relaxing factor.[16] In our studies substance P produced only weak endothelium dependent relaxation, which could be due to a differential density of receptors on the vein compared with other human vascular tissues or the low release of nitric oxide in saphenous veins as previously reported.[17]

Vasoactive intestinal peptide is a 28 amino acid peptide originally isolated from porcine intestine,[18] and subsequently found in the central nervous system and in peripheral nerves supplying many organs.[19] Its main physiological role has been postulated to be that of a local neurotransmitter.[20] It produces endothelium dependent dilatation of the rat aorta,[21 22] rabbit mesenteric artery,[23] and human coeliac artery.[24] By contrast, endothelium independent relaxation due to vasoactive intestinal peptide has been seen in cat cerebral arteries,[25] dog coronary arteries,[26] and human pulmonary arteries.[27] Our study showed endothelium dependent relaxation of isolated human saphenous vein in response to vasoactive intestinal peptide.

Calcitonin gene related peptide elicits only weak relaxation in the saphenous vein, apparently through a direct action on the vascular smooth muscle. This peptide is claimed to be the most potent endogenous vasodilator in human blood vessels.[28 29] It causes both endothelium dependent and endothelium independent relaxation.[7 30 31] Minor dilatation caused by calcitonin gene related peptide in the saphenous vein might be due to the absence of the endothelium-dependent relaxation mechanism.[7 31]

Neuropeptide Y is a 36 amino acid peptide that is found with noradrenaline in sympathetic neurones.[32] It has a direct vasoconstrictive action and may influence the action of noradrenaline as well as other transmitters in the control of vascular tone in many blood vessels.[33-35] Compared with other reported vasoconstrictors, neuropeptide Y and somatostatin induce only moderate contraction in the saphenous vein.[36] Furthermore, the constriction induced by somatostatin was greatly increased in the absence of endothelium, whereas that of neuropeptide Y was not affected. The difference between the responses to neuropeptide Y and somatostatin after removal of the endothelium may be explained by lack of basal secretion of endothelium derived relaxing factor by the saphenous vein[37] coupled with the ability of somatostatin but not neuropeptide Y to stimulate the release of the relaxing factor.

The concentrations of peptide used in this study are comparable with those used in in vitro studies of human mesenteric arteries and veins.[3] We avoided using high concentrations to enable better comparison with the concentrations of peptides circulating in the body to be made. Circulating concentrations of various peptides have been assayed in healthy patients: substance P and calcitonin gene related peptide concentrations have been measured at 1·2 (0·1) and 35·0 (4·0) pmol/l respectively,[38] and plasma vasoactive intestinal peptide concentration at 0·5–21 pmol/l.[39] It is difficult, however, to predict the local concentrations of these peptides at their receptors.

The sensitivity of the saphenous vein to these five neuropeptides differs from that of other human vascular tissues.[3 7] This further highlights the heterogeneity of the response of human blood vessels to vasoactive compounds. A similar heterogeneity between human arteries and veins has been reported for both endothelial function and the action of vasoconstrictors.[37 40 41] This difference in response could have important physiological and pathological implications.

Neuropeptides have been shown to be localised with neurotransmitters—for example, neuropeptide Y is stored with noradrenaline,[32] and acetylcholine and vasoactive intestinal peptide are present together in parasympathetic nerves.[42] As the saphenous vein is supplied in situ with both sympathetic and parasympathetic nerves, neuropeptides may act as neuromodulators[42] and play an integral part in the neuronal control of vascular smooth muscle tone before the vein is removed during surgery. Harvesting the saphenous vein for bypass grafting results in total denervation of the vessel. Hence the sensitivities of the endothelium and smooth muscle become the determinant factors in the action of neuropeptides when the vein is used as a bypass graft.

Evidence is increasing that saphenous vein grafts cannot be regarded as rigid tubes with little tendency for vasomotion.[43,44] Their dynamic properties could modulate blood flow and hence affect myocardial perfusion. We have characterised the action of certain vasoactive peptides on the isolated human saphenous vein and their possible dependence on endothelium. More studies are required to determine the exact role of neuropeptides in controlling flow in the saphenous vein before and after its use as a bypass graft and their possible effects on long term patency.

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1 Edvinsson L, Hakanson R, Sundler F, *et al.* Peptide-containing nerve fibres in human arteries and veins: vasomotor responses to the neuropeptides. In: Nobin A, Owman C, Arnek lo-Nobin B, eds. *Neuronal messengers in vascular function.* Amsterdam: Elsevier, 1987:199–209.
2 Pernow J. Actions of constrictor (neuropeptide Y and endothelin) and dilator (substance P, calcitonin gene-related peptide and vasoactive intestinal peptide) peptides on pig splenic and human skeletal muscle arteries: involvement of the endothelium. *Br J Pharmacol* 1989;97: 983–9.
3 Tornebrandt K, Nobin A, Owman C. Vasomotor effects of nine neuropeptides on isolated human mesenteric blood vessels. *Peptides* 1987;8:251–6.
4 Bassenenge E, Busse R. Endothelial modulation of coronary tone. *Pro Cardiovasc Dis* 1988;XXX:349–80.
5 Feletou M, Vanhoutte PM. Endothelium-dependent hyperpolarization of canine coronary smooth muscle. *Br J Pharmacol* 1988;93:515–24.
6 Yanagisawa M, Kurihara H, Kimura S, *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;332:411–5.
7 Thom SM, Hughes AD, Goldberg P, *et al.* The actions of calcitonin gene-related peptide and vasoactive intestinal peptide as vasodilators in man in vivo and in vitro. *Br J Clin Pharmacol* 1987;24:139–44.
8 Marshaw I, Al-Kazwini SJ, Holman JJ, *et al.* Human alphacalcitonin gene-related peptide is a potent vasodilator in human mesenteric vasculature. *Br J Clin Pharmacol* 1988;26:691–5.
9 Dain R, Kenchington G. Femoro-popliteal vein or proethetic bypass: which conduit is best after 3 years? In: Greenhalgh CW, Jamieson AN, Nicolaides WB, eds. *Limb salvage and amputation for vascular disease.* Philadelphia: WB Saunders, 1988:68–72.
10 Martling CR, Matran R, Alving K, *et al.* Innervation of lower airways and neuropeptide effects on bronchial and vascular tone in the pig. *Cell Tissue Res* 1990;260:223–33.
11 Lundberg JM, Fahrenkrug J, Hokfelt T, *et al.* Co-existence of peptide HI (PHI) and vasoactive intestinal peptide in nerves regulating blood flow and bronchial smooth muscle tone in various mammals including man. *Peptides* 1984; 5:593–606.
12 McEwan J, Larkin S, Davies G, *et al.* Calcitonin gene-related peptide: a potent dilator of human epicardial coronary arteries. *Circulation* 1986;74:1243–8.
13 Smitherman TC, Popma JJ, Said SI, *et al.* Coronary hemodynamic effects of intravenous vasoactive intestinal peptide in humans. *Am J Physiol* 1989;157:1254–62.
14 Chester AH, O'Neill GS, Moncada S, *et al.* Low basal and stimulated release of nitric oxide in atherosclerotic epicardial coronary arteries. *Lancet* 1990;336:897–900.
15 O'Neil GS, Chester AH, Allen SP, *et al.* Endothelial function of human gastroepiploic artery: implications for its use as a bypass graft. *J Thorac Cardiovasc Surg* 1991; 102:561–5.
16 Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;327:525–6.
17 Yang Z, Segesser LV, Bauer E, *et al.* Different activation of the endothelial L-arginine and cyclooxygenase pathway in the human internal mammary artery and saphenous vein. *Circ Res* 1991;68:52–60.
18 Said SI, Mutt V. Polypeptide with broad biological activity: avenisolation from small intestine. *Science* 1970;169: 1217–8.
19 Hokfelt T, Schultzberg M, Lundberg JM, *et al.* Distribution of vasoactive intestinal polypeptide in the central and peripheral nervous systems as revealed by immunocytochemistry. In: Said SI, ed. *Vasoactive intestinal peptide.* New York: Raven Press, 1982:65–90.
20 Larsson LI. Localization of vasoactive intestinal polypeptide: a critical appraisal. In: Said SI, ed. *Vasoactive intestinal peptide.* New York: Raven Press, 1982:51–63.
21 Sata T, Linden J, Liu LW, *et al.* Vasoactive intestinal peptide evokes endothelium-dependent relaxation and cyclic AMP accumulation in rat aorta. *Peptides* 1988; 9:853–8.
22 Davis JM, Williams KI. Endothelium-dependent relaxation effects of vasoactive intestinal polypeptide and arachidonic acid in rat aorta strips. *Prostaglandins* 1984;27:195–202.
23 Itoh T, Sasaguri T, Makita Y, *et al.* Mechanisms of vasodilation induced by vasoactive intestinal polypeptide in rabbit mesenteric artery. *Am J Physiol* 1985;249: 231–40.
24 Thom S, Hughes A, Martin G, *et al.* Endothelium-dependent relaxation in isolated human arteries and veins. *Clin Sci* 1987;73:547–52.
25 Edvinsson L, Fredholm BB, Hamel E, *et al.* Perivascular peptides relax cerebral arteries concomitant with stimulation of cyclic adenosine monophosphate accumulation or release of an endothelium-derived relaxing factor in the cat. *Neurosci Lett* 1985;58:213–7.
26 Brum JM, Go VMW, Vanhoutte PM, *et al.* Evidence for VIP-ergic control of coronary vasoregulation. *Regul Pept* 1985;3:37.
27 Sata T, Misra HP, Kubota E, *et al.* Vasoactive intestinal polypeptide relaxes pulmonary artery by an endothelium-independent mechanism. *Peptides* 1986;7:225–7.
28 Brain SD, Williams TJ, Tippins JR, *et al.* Calcitonin gene-related peptide is a potent vasodilator. *Nature* 1985;313: 54–6.
29 Struthers AD, Brown MJ, Macdonald DWR, *et al.* Human calcitonin gene-related peptide: a potent endogenous vasodilator in man. *Clin Sci* 1986;70:389.
30 Greenberg B, Rhoden K, Barnes P. Calcitonin gene-related peptide (CGRP) is a potent non-endothelium-dependent inhibitor of coronary vasomotor tone. *Br J Pharmacol* 1987;92:789–94.
31 MacCormack DG, Mak JCW, Coupe MO, Barnes PJ. Calcitonin gene-related peptide vasodilation of human pulmonary vessels. *Am J Physiol* 1989;67:1265–70.
32 Ekblad E, Evinsson L, Wahlestedt C, *et al.* Neuropeptide Y co-exists and co-operates with noradrenaline in perivascular nerve fibres. *Regul Pept* 1984;8:225–35.
33 Macho P, Perez R, Huidobro-Toro JP, Domenech RJ. Neuropeptide Y: a coronary vasoconstrictor and potentiator of catecholamine-induced coronary constriction. *Eur J Pharmacol* 1989;167:67–74.
34 Wahlestedt C, Edvinsson L, Ekblad E, Hakanson R. Neuropeptide Y potentiates noradrenaline-evoked vasoconstriction. Mode of action. *J Pharmacol Exp Ther* 1985;234:735–41.
35 Edvinsson L, Ekblad E, Hakanson R, Wahlestedt C. Neuropeptide Y potentiates the effects of various vasoconstrictor agents on rabbit blood vessels. *Br J Pharmacol* 1984;83:519–600.
36 Chester AH, Bodelsson M, Arnek lo-Nobin B, *et al.* Characterization of 5-HT receptors in the human saphenous vein, implications for patency of bypass grafts. *J Appl Cardiol* 1990;5:51–9.
37 Luscher TF, Diederich D, Siebenmann R, *et al.* Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med* 1988;319: 462–7.
38 Edvinsson L, Ekman R, Thulin T. Reduced levels of calcitonin gene-related peptide but not substance P during and after treatment of severe hypertension in man. *J Hum Hypertens* 1989;3:267–70.
39 Mitchell S, Bloom SR. Measurement of fasting and postprandial plasma vasoactive intestinal peptide in man. *Gut* 1978;19:1043–8.
40 Yang Z, Diederich D, Schneider K, *et al.* Endothelium-derived relaxing factor and protection against contractions induced by histamine and serotonin in the human internal mammary artery and in the saphenous vein. *Circulation* 1989;80:1041–8.
41 Weinstein JS, Grossman W, Weintraub RM, *et al.* Differences in a-adrenergic responsiveness between human internal mammary arteries and saphenous veins. *Circulation* 1989;79:1264–70.
42 Burnstock G. Mechanisms of interaction of peptide and nonpeptide vascular neurotransmitter systems. *J Cardiovasc Pharmacol* 1987;10:74–81.
43 Mann JM, McIntosh CL, Roberts WC. Spasm of saphenous veins used as conduits for aortocoronary by-pass grafting. *Am J Cardiol* 1987;15:1000–2.
44 D'Souza VJ, Velasquez G, Kahl FR, *et al.* Spasm of the aortocoronary venous graft. *Radiology* 1984;151:83–4.

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Regional blood flow in chronic heart failure: the reason for the lack of correlation between patients' exercise tolerance and cardiac output?

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Abstract

***Background*—In patients with chronic heart failure there is no relation between cardiac output and symptom limited exercise tolerance measured on a bicycle or treadmill. Furthermore, the increase in cardiac output in response to treatment may not be matched by a similar increase in exercise tolerance. More important in determining exercise capability is blood flow to skeletal muscle. This implies that the reduction in skeletal muscle blood flow is not directly proportional to the reduction in cardiac output and that there are regional differences in blood flow in patients with heart failure.**

***Methods*—Cardiac output and regional blood flow measured in 30 patients with chronic heart failure were compared with values obtained from 10 healthy controls. Measurements were made at rest and in response to treadmill exercise and were all made non-invasively.**

***Results*—Cardiac output was lower in the patients at rest and during exercise. Blood flow in the superior mesenteric and renal arteries was also lower in the patients and represented a different proportion of cardiac output than in the controls. In response to exercise the increase in blood flow to the calf and therefore to skeletal muscle, was reduced in the patients. In the patients there was no correlation between resting cardiac output and blood flow in the superior mesenteric artery, renal artery, or calf.**

***Conclusions*—Because blood flow to skeletal muscle and to the kidneys is likely to be important in determining patients' symptoms this factor may explain why central haemodynamic variables do not correlate with the exercise tolerance in patients with chronic heart failure.**

Peripheral vasoconstriction is well recognised in patients with chronic heart failure.[1] Venous vasoconstriction helps to maintain cardiac output by the Starling mechanism, while arterial vasoconstriction helps to maintain blood pressure in the face of a reduced cardiac output. Total systemic vascular resistance is therefore increased but because this is a measure of the summation of changes in all vascular beds it provides no information about local differences in arterial tone or regional blood flow.

One of the more interesting aspects of chronic heart failure is that the extent of cardiac dysfunction estimated from central haemodynamic variables bears no relation to the symptomatic impairment of patients assessed by treadmill exercise testing.[2] To explain this it has been suggested that the major cause of the limited exercise tolerance of patients is reduced blood flow to skeletal muscle.[3 4] Another vascular bed that is likely to be important in determining patients' symptoms is that of the kidneys. Control of salt and water excretion, and therefore plasma volume and tissue oedema, is intimately linked to both the perfusion pressure and blood flow to the kidneys.

If, as seems likely, the combination of cardiac output and arteriolar tone controls regional blood flow, knowledge of this would help in our understanding of heart failure and its response to treatment. The distribution of cardiac output has been described in healthy people and patients with heart failure.[5 6] These studies confirmed that there was a significant reduction in regional blood flow in the patients and the proposal was that this reduction in flow was in proportion to the reduction in cardiac output. However, the measurements were made with invasive techniques, which in themselves may alter haemodynamic variables.[7] This and the fact that the dye dilution measurements of regional blood flow cannot be readily repeated limit their usefulness in assessing patients' response to treatment. The purpose of this study was to investigate with non-invasive techniques cardiac output and regional blood flow at rest and in response to exercise in patients with chronic heart failure and compare the results with values obtained in healthy controls.

Patients and methods

PATIENTS

Thirty patients with chronic heart failure (New York Heart Association grade II–III) were studied. All had been in heart failure for at least six months. Their mean (SEM) age was 67 (2) years and 27 were men. Heart failure was caused by ischaemic heart disease in 23 patients, rheumatic heart disease with mitral regurgitation and impaired left ventricular function in four patients, and three patients had a dilated cardiomyopathy. All the patients were treated with at least 80 mg of frusemide daily and the mean dose was 156 mg (range 80–750 mg). In addition seven of the patients were taking captopril in a dose of at least 25 mg three times daily.

Ten volunteers with a mean (SEM) age of 49 (4) years were studied as healthy controls. Eight were men. All denied symptoms of heart failure and none had clinical evidence of heart failure. All had normal resting and exercise 12 lead electrocardiograms. None was taking any cardiovascular medication.

METHODS

Both the patients and controls were fully familiarised with the techniques on at least two occasions before being studied. Measurements of cardiac output and regional blood flow were then made after an overnight fast and at least 30 minutes of supine rest in a temperature controlled laboratory (23–24°C). Measurements were also made during a submaximal treadmill exercise test: the speed and slope of the treadmill were increased after four minutes at each of the following stages:

	Stage		
	I	II	III
Speed (km/h)	2·7	2·7	2·7
Slope (°)	0	1·3	2·6

Cardiac output

Cardiac output was measured by the indirect Fick principle and respiratory gases were monitored with a mass spectrometer (VG Medicals). Carbon dioxide was the indicator. Carbon dioxide production was calculated from minute ventilation and mixed expired carbon dioxide concentration, the partial pressure of carbon dioxide in pulmonary venous (systemic arterial) blood was derived from end tidal carbon dioxide concentration, and the partial pressure in mixed venous blood was measured after a rebreathing manoeuvre. These three variables were used to solve the Fick equation. The method has been shown to correlate closely with cardiac output measured by thermodilution.[8]

Cardiac output was measured with the patients sitting, standing, and at fixed submaximal workloads during the treadmill exercise test, at the end of stages I, and (if the patients were capable) at the end of stage III.

Blood flow in the superior mesenteric and renal arteries

Blood flows in the superior mesenteric artery[9 10] and right renal artery[11] were measured by transcutaneous Doppler ultrasound with a 5 kHz curvilinear ultrasound probe or with a sector scanner with an offset 2 kHz Doppler probe (Doptek). The vessels were identified by ultrasound and the sample volume of the pulsed Doppler system was adjusted to the size of the vessel being interrogated. Doppler spectral analysis was recorded onto a video tape with the subjects' breath being held in mid-inspiration. Mean values of time averaged velocity were taken from at least 10 Doppler waveform complexes. For patients in atrial fibrillation, the time averaged velocity was calculated from a minimum of 25 Doppler waveform complexes. The vessel diameter was calculated as the mean of four values. Measurements and Doppler signals were made from the proximal portion of each vessel. Blood flow was calculated as ml/min[12]

$$\frac{(\pi \times D^2 \times TAV \times 60)}{4}$$

where D is the vessel diameter and TAV the time averaged velocity.

Calf blood flow

Calf blood flow was measured by venous occlusion plethysmography with mercury in silastic strain gauges.[13] Measurements were made with the patients resting and from three to 13 minutes after a second exercise test. The workload was identical for both patients and controls.

Intraobserver variability

Within subject variability for all of the variables both in patients and controls was assessed by repeated measurements over the course of three weeks. All measurements were performed by the same investigator (AFM). The mean coefficients of variability for resting values in the patients were 7·8% for cardiac output, 7·5% for calf blood flow, 10·1% for blood flow in the superior mesenteric artery and 10·8% for blood flow in the right renal artery. Corresponding values for the controls were between 6·5 and 9·5%.

Statistical analysis

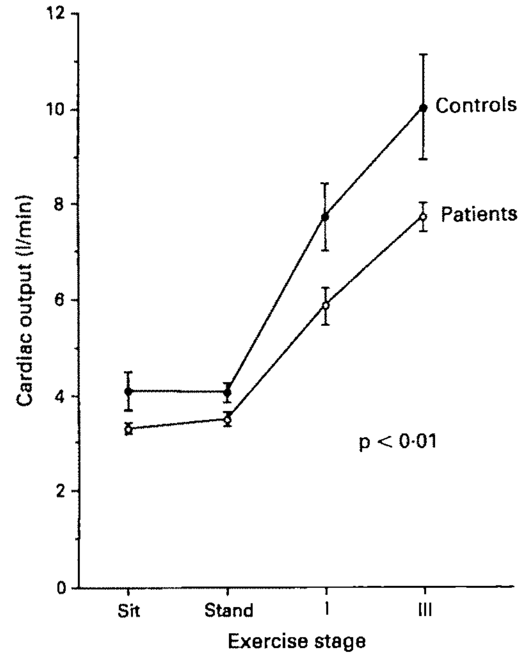
Differences in cardiac output and blood flow in the superior mesenteric and renal arteries were analysed by the Wilcoxon signed rank test; changes in calf blood flow and exercise cardiac output by analysis of variance for repeated measures (ANOVA); and correlations between cardiac output and regional blood flow by Pearson's moment correlation coefficient.

Results

CARDIAC OUTPUT

Figure 1 shows the mean (SEM) values of cardiac output for the patients and controls. Measurements were made in all the patients while they were sitting and standing, in 17 patients at the end of stage I of the exercise protocol, but in only eight patients at the end of stage III because the remainder were incapable of performing this amount of exercise. Sitting measurements were lower in the patients (3·3 (0·1) l/min) than the controls (4·1 (0·4) l/min) ($p < 0\cdot01$). This difference became greater during exercise and the mean value at the end of stage I for the patients was 5·9 (0·4) l/min compared with 7·7 (0·7) l/min in the controls, while at the end of stage III it was 7·6 (0·4)

Figure 1 Mean (SEM) values of resting and exercise cardiac output in the patients with heart failure and controls. Measurements were made in all patients and controls in the sitting and standing positions and in 17 patients at stage I and eight patients at stage III.



l/min for the patients and 10·0 (1·1) l/min for the controls (p < 0·01).

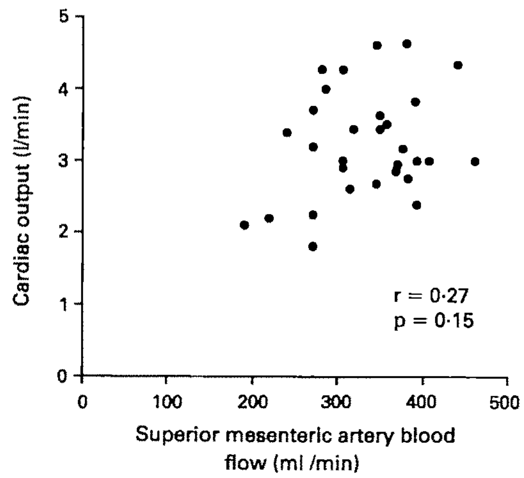
BLOOD FLOW IN THE SUPERIOR MESENTERIC ARTERY

Mean (SEM) resting values of blood flow in the superior mesenteric artery were 332 (12) ml/min in the patients compared with 446 (40) ml/min in the controls (p < 0·02). In the patients this was 9·8% of cardiac output whereas in the controls it was 10·8% of cardiac output. Figure 2 shows the relation between resting blood flow in the superior mesenteric artery and resting cardiac output in the patients. The relation between the two variables failed to reach significance (r = 0·27, p = 0·15).

BLOOD FLOW IN THE RENAL ARTERY

Satisfactory renal artery Doppler waveforms were obtained in only 15 of the patients. The mean (SEM) value of blood flow in the renal artery in the patients was 317 (26) ml/min compared with 452 (50) ml/min in the controls (p < 0·01). On the assumption that blood flow to both kidneys was the same, total renal blood flow represented 21·8% of cardiac output in the controls whereas it was 18·6% in the patients. Figure 3 shows the lack of relation between renal artery blood flow and cardiac output in the patients (r = 0·38, p = 0·12).

Figure 2 Relation between resting cardiac output and blood flow in the superior mesenteric artery in the patients with heart failure.



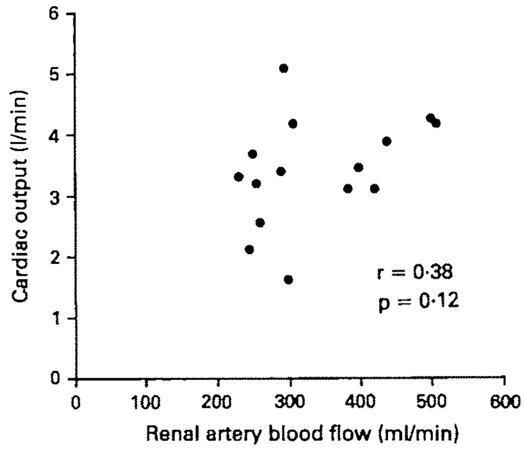


Figure 3 Relation between resting cardiac output and blood flow in the right renal artery in the 15 patients with heart failure in whom a satisfactory Doppler signal was obtained.

CALF BLOOD FLOW

The mean (SEM) values of resting calf blood flow in the patients was 1·9 (0·1) ml/100 ml/min whereas in the controls it was 2·7 (0·3) ml/100 ml/min, p < 0·05. Figure 4 shows the mean (SEM) values of calf blood flow at rest and from three to 13 minutes after a submaximal treadmill exercise test to a similar workload in the patients and the controls. Both groups showed the expected increase in calf blood flow after exercise but this was less in the patients than in the controls (p < 0·02).

Figure 5 shows the relation between resting values of cardiac output and calf blood flow in the patients. Again there was no obvious relation between these two variables (r = 0·32, p = 0·09).

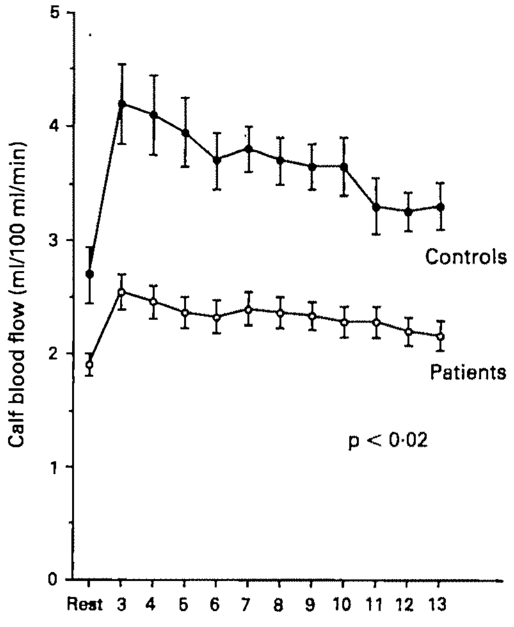


Figure 4 Mean (SEM) values of calf blood flow at rest and from 3 to 13 minutes after a fixed submaximal exercise workload in 30 patients with heart failure and controls.

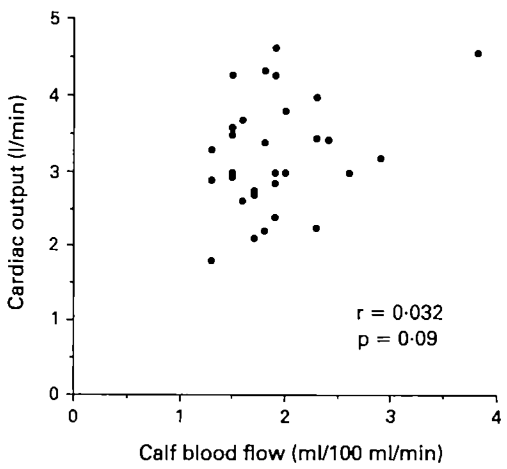


Figure 5 Relation between resting cardiac output and calf blood flow in patients.

Discussion

In this study we simultaneously measured cardiac output and regional blood flow in a group of patients with severe heart failure and compared the results with those in healthy controls. All the measurements were performed non-invasively. We showed, not surprisingly, that the patients with heart failure had lower values of cardiac output at rest and that the increase in cardiac output in response to low levels of treadmill exercise was considerably less than the controls. We also showed that blood flow to the gut, kidneys, and limbs was reduced in the patients.

It might be expected that the reduced cardiac output of patients with heart failure would lead to the same reduction in blood flow to all organs. This does not seem to be the case and there is differential redirection of the cardiac output in heart failure. Not only were the absolute values of blood flow to the tissues reduced, but the proportion of cardiac output to the gut and kidneys was also reduced in the patients compared with the controls. This presumably occurs to maintain blood flow to the cerebral and coronary beds. Similarly blood flow to the calf, which consists predominantly of skeletal muscle, was also reduced at rest and after exercise. We did not assess the other regional blood flow responses to exercise, but others have shown an expected reduction in blood flow to the superior mesenteric artery after exercise.[14]

There was no significant correlation between cardiac output and any of the measurements of regional blood flow. This indicates the importance of local factors in controlling regional blood flow. It also indicates why cardiac output does not correlate with patients' symptomatic impairment. Because blood flow to skeletal muscle is important in determining patients' symptoms the lack of correlation between limb blood flow and cardiac output helps to explain the lack of correlation between cardiac output and symptomatic impairment. The other major cause of symptoms is likely to be fluid retention and this is in part governed by renal blood flow. Again a lack of correlation between renal blood flow and cardiac output may also help to explain the apparent lack of importance of cardiac output in determining patients' symptoms. Our results confirm the considerable reduction in regional blood flow reported elsewhere,[5] although we did not show any relation between cardiac output and regional blood flow. However, the correlations previously described[5] may have been spurious because they relied upon an analysis across two distinct groups, healthy controls and patients, and were not confined to the patients. Furthermore, those results were obtained with invasive techniques which in themselves are known to alter haemodynamic variables.

Although the absolute values of cardiac output may not be important in determining symptoms it is likely that any treatment that has a beneficial effect will need to increase cardiac output. If symptomatic improvement is dependent upon increasing renal and skeletal muscle blood flow then this will be most likely to occur only by an increase in cardiac output and not by further redistribution of cardiac output. The measurement of regional blood flow and cardiac output is likely therefore to be useful in evaluating new treatments for heart failure. Heart failure is characterised by important abnormalities of cardiac output and regional blood flow. Further investigation of these abnormalities will give us a better understanding of the pathophysiology of the disease. The use of non-invasive techniques similar to those we have described will permit measurements to be made in more patients with mild heart failure in whom invasive measurements may not be clinically justified and it will also permit frequent serial measurements to be made of the response to treatment.

1 Cohn JN. Physiologic basis for vasodilator therapy for heart failure. *Am J Med* 1981;71:135–9.
2 Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol* 1981;47:33–9.
3 Cowley AJ, Rowley JM, Stainer K, Hampton JR. Effects of captopril on abnormalities of the peripheral circulation and respiratory function in patients with severe heart failure. *Lancet* 1984;ii:1120–4.
4 Wilson JR, Martin JL, Schwarty D, Ferraro N. Exercise tolerance inpatients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. *Circulation* 1984;71:57–62.
5 Leithe ME, Margorien RD, Hermiller JB, Unverferth DV, Leier CV. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. *Circulation* 1984;69:57–64.
6 Mason DT, Zelis R, Longhurst J, Lee G. Cardiocirculatory responses to muscular exercise in congestive heart failure. *Prog Cardiovasc Dis* 1977;6:475–89.
7 Packer M, Medina N, Yusak M. Haemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterisation in patients with chronic heart failure. *Circulation* 1985;71:761–6.
8 Cowley AJ, Stainer K, Murphy DT, Murphy J, Hampton JR. A non invasive method for measuring cardiac output: the effect of Christmas lunch. *Lancet* 1986;ii:1422–4.
9 Qamar MI, Read AE, Skidmore R, Evans JM, Wells PNT. Transcutaneous Doppler ultrasound measurement of superior mesenteric artery blood flow in man. *Gut* 1986; 27:100–95.
10 Jager K, Bollinger A, Valli C, Ammann R. Measurement of mesenteric blood flow by duplex scanning. *J Vasc Surg* 1986;3:462–9.
11 Avasthi PS, Greene ER, Voyles WF. Noninvasive Doppler assessment of human postprandial renal blood flow and cardiac output. *Am J Physiol* 1987;252:F1167–F74.
12 Gill RW. Measurement of blood flow by ultrasound: accuracy and sources of error. *Ultrasound Med Biol* 1985; 11:625–41.
13 Whitney RJ. The measurement of volume changes in human limbs. *J Physiol* 1953;121:1–27.
14 Qamar MI, Read AE. Effects of exercise on mesenteric blood flow in man. *Gut* 1987;28:583–7.

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Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function

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Abstract

Background—Activation of the sympathetic nervous system has been extensively studied in patients with chronic heart failure, but the parasympathetic nervous system has received relatively little attention. The objective in this study was to investigate cardiac parasympathetic activity in chronic heart failure and to explore its relation to left ventricular function.

Methods—Heart rate variability was measured from 24 hour ambulatory electrocardiograms by counting the number of times each RR interval exceeded the preceding RR interval by more than 50 ms (counts). This method provided a sensitive index of cardiac parasympathetic activity.

Results—Mean (range) of counts were: waking 48 (1–275)/h, sleeping 62 (0–360)/h, and total 1310 (31–7278)/24 h. These were lower than expected, and in 26 (60%) of the 43 patients counts fell below the lower 95% confidence intervals (95% CI) for RR counts in normal subjects. A significant correlation between total 24 hour RR counts and left ventricular ejection fraction was present ($r = 0.49$, $p < 0.05$).

Conclusions—These results indicate that most patients with chronic heart failure have reduced heart rate variability and therefore reduced cardiac parasympathetic activity. The degree of parasympathetic dysfunction is related to the severity of left ventricular dysfunction. This may be relevant to the high incidence of ventricular arrhythmias and poor prognosis of patients with chronic heart failure.

Unlike most other diseases of the cardiovascular system, the incidence and prevalence of chronic heart failure is rising in the Western world.[1 2] Chronic heart failure is therefore an increasing cause of disability and death in the community.

Autonomic control of the cardiovascular system is deranged in chronic heart failure and contributes to the pathophysiology of the syndrome.[3] The sympathetic nervous system has been widely studied and its activity is enhanced in chronic heart failure.[4] The amount of sympathetic activation is linked to symptoms[5] and haemodynamic indices of impaired left ventricular function.[6 7] Although the sympathetic nervous system is activated in chronic heart failure, reflex changes in autonomic activity during stress are impaired.[8 9] Increasing sympathetic activation is associated with a progressive rise in afterload leading to a deterioration in myocardial pump function[7 10 11] and has an inverse relation with survival.[12] Although abnormal parasympathetic function has also been found in chronic heart failure, this has not been extensively studied.[13 14]

Analysis of variability of heart rate has been developed over the last decade as a useful non-invasive way of measuring activity of the autonomic nervous system. We have developed a method, with 24 hour electrocardiograms, that is a reliable and a specific index of cardiac parasympathetic function,[15] and is valid even in the presence of frequent ventricular extrasystoles.[16]

Our aims in this study were to determine whether abnormal cardiac parasympathetic activity is present in patients with chronic heart failure and to examine the relation between resting left ventricular function and cardiac parasympathetic function.

Patients and methods

PATIENTS WITH CHRONIC HEART FAILURE

Sixty ambulatory patients (42 men) with chronic heart failure due to ischaemic heart disease were studied. Their mean age was 61 (range 36–72), and all had moderate limitation of their daily activities, categorised as grade II or III of the New York Heart Association (NYHA) classification. Resting left ventricular function was impaired in all patients. This was assessed by a standard radionuclide technique for calculation of ejection fraction.[17] The mean (range) ejection fraction of patients was 17·8 (5–35)%. All patients were in sinus rhythm.

Patients were receiving only diuretics to control their chronic heart failure, with a mean (range) frusemide dose of 102 (40–160) mg. No patient had diabetes or renal failure and their clinical state had been stable for at least three months before the study. No patient had any history or clinical evidence of autonomic neuropathy. Because a recent myocardial infarction may affect cardiac parasympathetic activity, we excluded all patients with a documented myocardial infarction during the previous six months.

Tapes from 17 patients were excluded from analysis because of the presence of frequent supraventricular extrasystoles or technical problems with tape quality. There were no significant differences in baseline characteristics between the 43 patients (30 men, 13 women) included and the 17 patients (12 men, five women) excluded from further study.

METHODS

Electrocardiograms were obtained with a miniature tape recorder (Tracker, Reynolds Medical Limited) for 24 hours from all patients during normal ambulant out of hospital activities. Times of going to bed and getting up were noted by the patients.

Tapes were replayed through a Pathfinder arrhythmia analyser (Reynolds Medical Limited) at 120 times the original recording speed. Heart rate variability was then assessed by the count based time domain method we have previously described.[15 16] Briefly, each RR interval was measured and successive beat by beat RR interval differences calculated. Each time an RR interval exceeded the preceding interval by more than 50 milliseconds a count was registered. Counts were accumulated and the results presented as total 24 hour RR counts, mean hourly waking RR counts, mean hourly sleeping RR counts, and mean waking and sleeping heart rates.

Segments of tape in which changes in RR intervals occurred due to the presence of ventricular extrasystoles were excluded from analysis by the Pathfinder arrhythmia analyser, which detected ventricular extrasystoles due to the difference in their morphology and timing.[16 18] As the Pathfinder arrhythmia analyser is unable to detect atrial arrhythmias, the signal was also closely monitored by the operator and tapes in which atrial arrhythmias occurred were discarded. Where less than 24 hours of recording were available for analysis, the results were normalised to the equivalent of 24 hours. Recordings shorter than 18 hours or with less than 40% of the tape suitable for analysis were rejected.

We have already defined normal age related 95% confidence intervals (95% CI) for counts with the same equipment and technique.[19] Values obtained from patients with chronic heart failure have been compared with this normal range.

We have discussed the reasons why our technique provides a measure of cardiac parasympathetic activity.[15 20] Abrupt changes in RR interval that occur at the start of muscular exercise, standing up, or lying down, are mediated by the vagus nerve.[21-23] Variation in RR interval is abolished in animals by cutting the vagus nerve[24] and in humans by parasympathetic blockade with atropine,[20] but is unaffected by β adrenoreceptor blockade.[15] Patients with transplanted hearts and diabetic patients with cardiovascular reflex evidence of vagal damage have very little variability in RR interval as measured by our technique.[15] Also, animal studies suggest that the degree of respiratory sinus arrhythmia is directly related to vagal efferent activity.[25-27]

Our method also correlates well with the high frequency (> 0·15 Hz) band of the power spectrum,[28] which is thought to be mediated by cardiac parasympathetic pathways.[29 30] Our method is probably more specific as a measure of cardiac parasympathetic activity than other commonly used time domain methods.[28] RR interval counts that fall below the normal lower 95% CI therefore represent reduced cardiac parasympathetic activity.

STATISTICAL ANALYSIS

Because the RR counts are not normally distributed data were log transformed before analysis. A simple linear regression was used to investigate the relation between total 24 hour RR counts and ejection fraction. Counts are expressed as geometric mean (range). Heart rates are expressed as arithmetic mean (SD).

Results

HEART RATE VARIABILITY

Group mean (range) counts of RR interval changes were; waking 48 (1–275)/h sleeping 62 (0–360)/h, and total 1310 (31–7278)/24 h. Counts were lower than the predicted mean values for normal subjects of the same mean age of 61 years (waking 72, sleeping 122, and total 2512). Figure 1 depicts total 24 hour RR counts plotted against age. Twenty six of the 43 patients fell below the lower 95% CI for normal subjects. Mean waking (85 (14) beats per min) and sleeping (77 (15) beats per min) were normal.

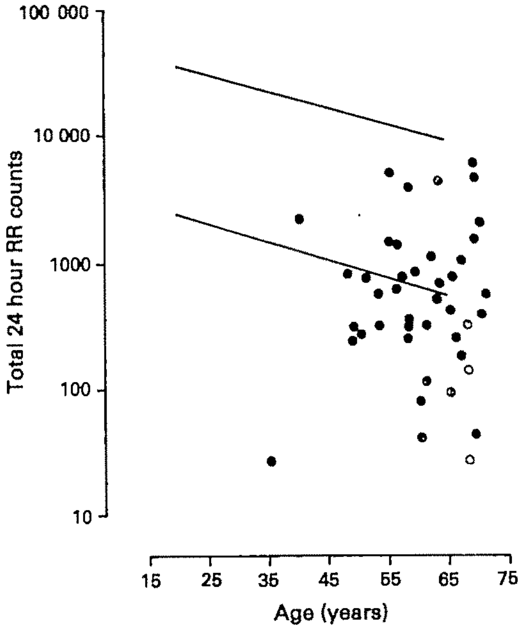

Figure 1 Total 24 hour counts of RR interval changes plotted against age. Solid lines represent 95% confidence intervals (95% CI) for counts in normal subjects. Twenty six of the 43 patients with chronic heart failure had values below the lower 95% CI.

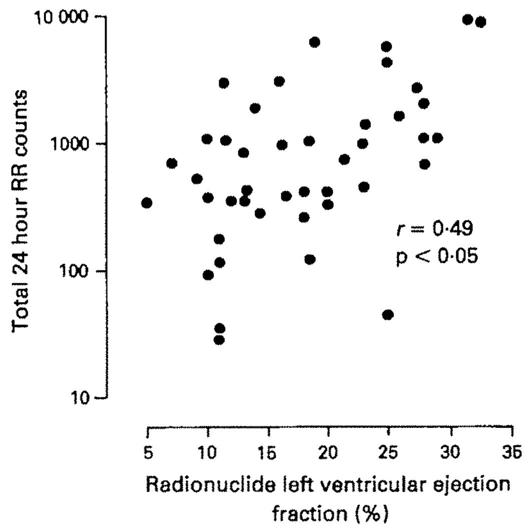

Figure 2 Total 24 hour counts of RR interval changes plotted against radionuclide ejection fraction. A significant relation exists, with the lowest counts obtained in those patients with the most severe impairment of left ventricular function.

RELATION BETWEEN HEART RATE VARIABILITY AND LEFT VENTRICULAR FUNCTION

Figure 2 shows the relation between total 24 hour RR counts and left ventricular ejection fraction. A significant linear correlation was found with the lowest counts obtained in the patients with the greatest impairment of left ventricular function ($r = 0{\cdot}49$, $p < 0{\cdot}05$).

Discussion

We have shown in our study that most of our patients with chronic heart failure due to ischaemic heart disease have reduced heart rate variability and by inference, therefore, reduced cardiac parasympathetic activity. Also, we have shown that a significant relation exists between the severity of left ventricular dysfunction and the extent of parasympathetic impairment. These findings have a number of potential implications.

Previous studies have shown that sympathetic activation occurs in chronic heart failure,[4] initially as a compensatory mechanism to maintain adequate central blood pressure.[31] The role of the parasympathetic nervous system in the pathophysiology and prognosis of chronic heart failure has not been studied in depth. Two previous studies of heart rate variability in chronic heart failure, one using power spectral analysis,[32] and the other a standard deviation method of analysis,[33] show a similar pattern of reduced heart rate variability but suffer from certain drawbacks. Standard deviation methods do not clearly differentiate between sympathetic and parasympathetic influences. Power spectral analysis, unlike our method, is rendered unreliable in the presence of ventricular extrasystoles, which occur frequently in patients with chronic heart failure. Our method is specific as a measure of parasympathetic function and clearly shows that impaired cardiac parasympathetic activity occurs throughout the 24 hour period.[15,16,19,20,28]

Both resting left ventricular function and the amount of sympathetic activation are linked to prognosis in patients with chronic heart failure.[12,34,35] Patients with severe impairment of left ventricular function have maximal activation of the sympathetic system. We have shown that a similar relation exists for impaired parasympathetic function.

There are several potential mechanisms to explain the abnormalities we found. The renin angiotensin system is activated in patients with symptomatic chronic heart failure of NYHA grade II and greater treated with diuretics,[4,36,37] and there is evidence that the amount of this activation is proportional to the clinical severity of the heart failure.[38] Angiotensin II is known to interact both centrally and peripherally with the autonomic nervous system to enhance sympathetic[39,40] and inhibit parasympathetic activity.[41,42] Increasing neuroendocrine activation in patients with chronic heart failure may therefore explain the presence of parasympathetic impairment and its relation to impaired left ventricular function. An alternative or additional mechanism in patients with ischaemic heart disease could be direct injury to intracardiac nerves and receptors, leading to disruption of autonomic reflexes. We have previously shown that parasympathetic impairment occurs early in the course of anterior myocardial infarction.[20] As chronic heart failure is more likely to occur after anterior than inferior infarction, this lends support to direct damage as a possible mechanism for original parasympathetic impairment in these patients, with increasing neuroendocrine activation contributing to progressive changes in those patients whose left ventricular function declines with time.

Sudden death occurs in almost 50% of patients with chronic heart failure.[2,43] Autonomic imbalance is known to be linked to the production of ventricular arrhythmias that are thought to be the cause of sudden death in most patients with chronic heart failure.[44-46] The reduction of parasympathetic activity that we have shown to occur in the presence of sympathetic overactivity, may therefore provide suitable conditions for the production of ventricular arrhythmias. We have already investigated the role of the angiotensin converting enzyme inhibitor captopril in regulating parasympathetic activity in chronic heart failure.[47] Captopril is known to have a beneficial effect on the incidence of ventricular arrhythmias[48] and sudden death in chronic heart failure.[49] The increase in parasympathetic activity that we demonstrated along with the reduction in sympathetic activity that is known to occur with captopril treatment, may be relevant to these effects.

We have also studied the effect of class I and class III antiarrhythmic drugs, commonly used in the treatment of ventricular arrhythmias in patients with chronic heart failure.[16] Some class I agents reduce cardiac parasympathetic activity and this may be an important factor in the adverse effect on prognosis that can occur when class I agents are used to treat ventricular arrhythmias in patients with impaired ventricular function.[50] By contrast, the class III agent amiodarone does not reduce cardiac parasympathetic activity. This may explain why this agent does not have an adverse effect[51] and may improve survival[52] when used to treat ventricular arrhythmias in chronic heart failure.

In conclusion, we have shown that cardiac parasympathetic activity is reduced in most patients with chronic heart failure and that the magnitude of this reduction is correlated with the severity of left ventricular impairment. Reduced heart rate variability is a powerful independent risk factor for sudden death in survivors of myocardial infarction.[53] Long term follow up studies of patients with chronic heart failure are now needed to find out whether reduced heart rate variability will have a similar predictive value in these patients.

1 Ghali JK, Cooper R, Ford E. Trends in hospitalization rates for heart failure in the United States 1973–1986: evidence for increasing population prevalence. *Arch Intern Med* 1990;150:769–73.

2 McFate Smith W. Epidemiology of congestive heart failure. *Am J Cardiol* 1985;55:3A–8.

3 Thomas P, Sheridan DJ. Pathophysiology of autonomic dysregulation in heart failure. In: Bannister R, ed. *Autonomic Failure. A textbook of disorders of the autonomic nervous system.* 2nd ed. Oxford: Oxford University Press, 1988:97–112.

4 Mancia G. Neurohormonal activation in congestive heart failure. *Am Heart J* 1990;120:1532–7.

5 Thomas AJ, Marks BH. Plasma norepinephrine in congestive cardiac failure. *Am J Cardiol* 1978;41:233–43.

6 Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to haemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659–66.

7 Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 1982;104:725–31.

8 Levine TB, Francis GS, Goldsmith SR, Cohn JN. The neurohumeral and haemodynamic response to orthostatic tilt in patients with congestive heart failure. *Circulation* 1983;67:1070–5.

9 Cody RJ, Franklin KW, Kluger J, Laragh JH. Mechanisms governing the postural response and baroreceptor abnormalities in chronic congestive heart failure: effects of acute and long term converting enzyme inhibition. *Circulation* 1982;66:135–42.

10 Dzau VJ, Hollenbery NK, Williams GH. Neurohormonal mechanisms in heart failure: role in pathogenesis, therapy, and drug tolerance. *Federation Proceedings* 1983;42: 3162–9.

11 Francis GW, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to haemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659–66.

12 Cohn JN, Levine TB, Olivari MT, Carberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:119–23.

13 Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877–83.

14 Goldstein RE, Beiser GD, Stampfer M, Epstein SE. Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. *Circ Res* 1975;36: 571–8.

15 Ewing DJ, Neilson JMN, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *Br Heart J* 1984;52:396–402.

16 Zuanetti G, Latini R, Neilson JMM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with cardiac arrhythmias: effect of antiarrhythmic drugs. *J Am Coll Cardiol* 1991;17:604–12.

17 Wathen CG, Muir AL, Hannan WJ. Radionuclide studies of left ventricular function in normal subjects. *Nucl Med Commun* 1990;11:607–15.

18 Neilson JMN. Computer detection of ventricular ectopic beats: On line and off. In: *Computers in cardiology*. Los Alamitos: IEEE Computer Society Press, 1975:33–5.

19 Ewing DJ, Neilson JMM, Shapiro CM, Steward JA, Reid W. 24 hour heart rate variability: effects of posture, sleep and time of day in normal subjects and comparison with bedside autonomic function tests in diabetic patients. *Br Heart J* 1991;65:239–44.

20 McAreavey D, Neilson JMM, Ewing DJ, Russell DC. Cardiac parasympathetic activity during the early hours of acute myocardial infarction. *Br Heart J* 1989;62:165–70.

21 Fagraeus L, Linnarsson D. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. *J Appl Physiol* 1976;40:679–82.

22 Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. *J Appl Physiol* 1980;49:809–14.

23 Bellavere F, Ewing DJ. Autonomic control of the immediate heart rate response to lying down. *Clin Sci* 1982;62:57–64.

24 Samaan A. The antagonistic cardiac nerves and heart rate. *J Physiol* 1935;83:332–40.

25 Katona PG, Tih F. Respiratory sinus arrhythmias: non-invasive measure of parasympathetic cardiac control. *J Appl Physiol* 1975;39:801–5.

26 Eckberg DL. Human sinus arrhythmias as an index of vagal cardiac outflow. *J Appl Physiol* 1983;54:961–6.

27 Eckberg DL. Parasympathetic cardiovascular control in human disease: a review of methods and results. *Am J Physiol* 1980;239:H581–93.

28 Myers GA, Martin GJ, Magid NM, Barnett PS, Schaad JW, Weis JS, Lesch M, Singer DH. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *Trans Biomed Eng* 1986;33:1149–56.

29 Askelrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213:220–3.

30 Pomeranz B, Macauley RJB, Caudill MA, Kutz I, Adam D, Gordon D, *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248:H151–3.

31 Zelis R, Mason DT. Compensatory mechanisms in congestive heart failure — the role of the peripheral resistance vessels. *N Engl J Med* 1970;282:962–4.

32 Saul JP, Yutaka A, Berger RD, Lilly LS, Collucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol* 1988;61:1292–9.

33 Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. *Am J Cardiol* 1989;64:1162–7.

34 Unverferth DV, Magorien DR, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147–52.

35 Schwarz F, Mall G, Zebe H, Schmitzer E, Martley J, Scheurien H, Kübler W. Determinants of survival in patients with congestive cardiomyopathy: quantitative morphological findings and left ventricular haemodynamics. *Circulation* 1984;70:923–8.

36 Genest J, Granger P, De Champlain J, Boucher R. Endocrine factors in congestive heart failure. *Am J Cardiol* 1968;22:35–42.

37 Laragh JH. Endocrine mechanisms in congestive heart failure. Renin, aldosterone and atrial naturetic hormone. *Drugs* 1986;32(suppl 5):1–12.

38 Dzau VJ, Colucci WS, Hollenbery NK, Williams GH. Relation of the renin-angiotensin aldosterone system to clinical state in congestive heart failure. *Circulation* 1981;63:645–51.

39 De Jonge A, Knape JTA, Van Meel JCA, *et al.* Effect of captopril on the sympathetic neurotransmission in pithed normotensive rats. *Eur J Pharmacol* 1983;88:231–5.

40 Zimmerman BG. Adrenergic facilitation by angiotensin: does it serve a physiological purpose. *Clin Sci* 1981;60:343–4.

41 Potter EK. Angiotensin inhibits the action of the vagus nerve at the heart. *Br J Pharmacol* 1982;75:9–11.

42 Lumbers ER, McCluskey DI, Potter EK. Inhibition by angiotensin II of baroreceptor evoked activity in cardiac vagal efferent nerves. *J Physiol* 1979;294:69–80.

43 Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;72:681–5.

44 Schwartz PJ. Sympathetic imbalance and cardiac arrhythmias. In: Randall WC (ed). *Nervous Control of Cardiovascular Function*. Oxford: Oxford University Press 1984:225–52.

45 Verrier RL, Lown B. Sympathetic parasympathetic interactions and ventricular electrical stability. In: Schwartz PJ, Brown AM, Malliani A, Zanchetti A, eds. *Neural Mechanisms in Cardiac Arrhythmias*. New York: Raven Press, 1977:75–86.

46 McAreavey D, Neilson JMN, Russell DC. Evidence for reduced vagal tone preceding ventricular fibrillation in man. *Eur J Clin Invest* 1986;16:A5.

47 Flapan AD, Nolan J, Neilson JMM, Ewing DJ. Captopril therapy increases parasympathetic activity in patients with congestive cardiac failure. *Circulation* 1990;82(suppl III):382.

48 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, *et al.* Captopril in heart failure—a double blind controlled trial. *Br Heart J* 1984;52:530–5.

49 Newman TJ, Maskin CS, Dennick LG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *Am J Med* 1988;84:140–44.

50 The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report. Effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. *New Engl J Med* 1989;321:406–12.

51 Stewart RA, McKenna WJ, Poloniecki JD, Michelson JK, Das SK, Morady F, *et al.* Prospective randomised double blind placebo controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular extra systoles. *Br Heart J* 1989;61(S):459–60.

52 Cleland JFG, Dargie HJ, Findlay IN, Wilson JT. Clinical haemodynamic and anti arrhythmic effects of long term treatment with amiodarone of patients in heart failure. *Br Heart J* 1987;57:436–45.

53 Kleiger RE, Miller JP, Bigger JT, Moss AJ. Multicentre post infection research group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–62.

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Lack of variation in venous tone potentiates vasovagal syncope

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Abstract

***Objective*—To investigate the peripheral venous response to head up tilting in malignant vasovagal syndrome.**

***Patients*—31 Patients with unexplained syncope or dizziness referred from the cardiology department.**

***Methods*—Changes in calf venous volume were studied by a radionuclide technique during 45° head up tilt testing.**

***Results*—During tilt testing six patients became syncopal but 25 were symptom free. The syncopal group had greater increases in calf venous volume after the change in posture and perhaps more importantly considerably less variability in the venous volume during the tilted period.**

***Conclusions*—The venous response was different in the syncopal patients. The lack of response of the peripheral venous circulation to changes in the central circulation may be responsible for triggering the Bezold-Jarisch reflex and malignant vasovagal syncope.**

Vasovagal syncope is a heterogenous condition. In a simple faint an external sensory stimulus—for example, sight of blood or venepuncture—causes the vagal response. Other forms of vasovagal syncope exist that result from stimulation of the Bezold-Jarisch reflex.[1] In these patients very low ventricular volumes result in a relatively empty ventricle contracting against itself and so generating very high intraventricular pressures. It is these high pressures that stimulate the Bezold-Jarisch reflex that causes parasympathetic activation and sympathetic withdrawal. This culminates in syncope due to hypotension and bradycardia. Several different circumstances can cause a very low central venous pressure and so provoke this chain of events. These include the administration of venodilator drugs—for example, glyceryl trinitate and amyl nitrite—and massive rapid haemorrhage.[2-4] Also the same reflex is thought to be responsible for the condition called either malignant vasovagal syndrome or neurally mediated syncope in which patients have recurrent syncope both without warning and without precipitating stimuli.[5 6] It is not understood why this occurs. Is it that they have a low threshold to initiation of the Bezold-Jarisch reflex or do they have an abnormality in their venous compartment that predisposes them to very low central pressures and this "empty heart syndrome"?

In this study we examined the changes in the peripheral venous blood volume during a head up tilt test and made correlations with the haemodynamic changes found. We used a radionuclide technique to monitor the changes in peripheral venous volume minute by minute after the change in posture.[7 8] We describe abnormalities that were associated with syncope and blood pressure changes.

Patients and methods

PATIENTS

All 31 patients (19 men, 12 women; age range 18–79) were referred for head up tilt testing as part of our investigation of unexplained syncope or dizziness. They included eight people with ischaemic heart disease (three with previous myocardial infarcts) and eight who were taking vasoactive medication—namely, β blockers, calcium antagonists, or nitrates. Earlier investigation was limited but all patients had undergone 24 hour Holter electrocardiographic monitoring and carotid sinus massage before referral and these tests had not explained the subject's episodes of syncope. No patient was assessed by electrophysiological study. Before participating in the study all patients gave informed consent.

MEASUREMENTS

The heart rate and rhythm were recorded continuously with a four channel electrocardiograph (Mingograf 34, Sweden) and monitor (Rigel DM721, Rigel Research, Surrey). Blood pressure was measured by a semiautomatic sphygmomanometer (Copal UA-251 digital, Japan) placed on the left arm. A radionuclide labelled blood pool was established by a semi in vitro technique.[9] Red blood cells labelled with 50 MBq technetium-99m were reinjected into the left arm and were allowed to reach equilibrium (10 minutes). Activity was detected by a caesium iodide crystal (John Caunt Scientific Ltd, Oxon), which was placed 5 cm from the skin of the right calf and was supported by a foam pad. Patients were asked not to move their legs during the study. Also, the crystal was clamped to the tilt table to prevent movement of the probe on tilting. The left leg was shielded with lead to prevent activity from this side contaminating the recordings from the right leg. The detector output was recorded and processed by a custom made nucleonics system con-

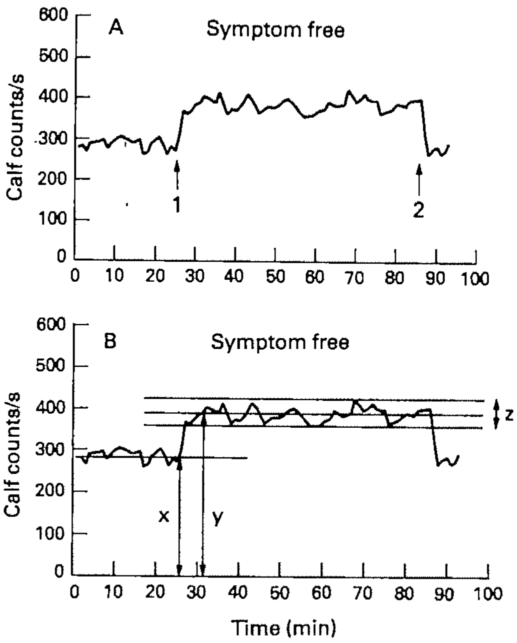


Figure 1 (A) Time activity curve from a symptom free patient. At time 1 the table was tilted and at time 2 it was returned to horizontal. (B) Same time activity curve with construction lines added. Percentage increase in venous volume $= \frac{y-x}{x} \times 100$. *Venous variability (%)* $= \frac{z}{y} \times 100$.

trolled by a microprocessor. Time activity curves were drawn and variables were derived after drawing construction lines (fig 1). The increase in venous volume (%) was derived by the formula: $(y - x)/x \times 100$ and the venous variability (%) was calculated by $z/y \times 100$. The time to plateau response is the time between lines x and y.

PROTOCOL

The patients had a light breakfast on the morning of the study. They were asked to continue their usual medication. The patient was positioned on the table and the measuring devices were set in place. Baseline recordings were made every five minutes over a 20 minute period with the table horizontal. The table was then tilted by a hand driven mechanism to 45° and maintained in this position for one hour or until the subject developed symptoms. When syncope or near syncope developed the table was returned to horizontal. Over the first five minutes of tilting haemodynamic recordings were made every minute, and between five and 10 minutes the rate was decreased to every two minutes. After 10 minutes of tilting, heart rate and blood pressure were documented every three minutes. If symptoms developed the recordings were repeated immediately.

STATISTICS AND ANALYSIS

The baseline haemodynamic measurements were the average of the recordings at five, 10, and 15 minutes when the patient was horizontal. The haemodynamic and venous response data in the two groups were compared by the non-parametric Mann-Whitney U test (Minitab 6.1 release, Minitab Inc). Correlation coefficients (Pearson moment product) were derived to assess associations between variables (Minitab 6.1 release, Minitab Inc).

Results

Patients were divided into two groups on the basis of their response to the tilt test: those that experienced syncope or near syncope (tilt positive) (n = 6) and those that remained symptom free (tilt negative) (n = 25). The age range of the group with symptoms was 60 to 77 years. To eliminate some of the effects of age on the cardiovascular response to tilting, analysis was also performed to include only those over age 55 in the symptom free group (n = 13).

BASELINE CHARACTERISTICS

Despite the differing age ranges of the groups with and without symptoms there were no significant differences in the age, sex, or haemodynamic variables at baseline (table). More people had ischaemic heart disease and were taking vasoactive medication in the symptom free group than in the group with symptoms but this difference was not statistically significant.

HAEMODYNAMIC RECORDINGS DURING TILT

The lowest recorded systolic blood pressure during head up tilt was significantly less in the syncopal group (mean (SD) 75·5 (19) *v* 124 (23) mm Hg $p = 0{\cdot}001$) and the maximum fall in systolic pressure from baseline to lowest level during the tilt test was significantly greater in the patients with symptoms (66 (23) *v* 14 (12) mm Hg $p < 0{\cdot}001$).

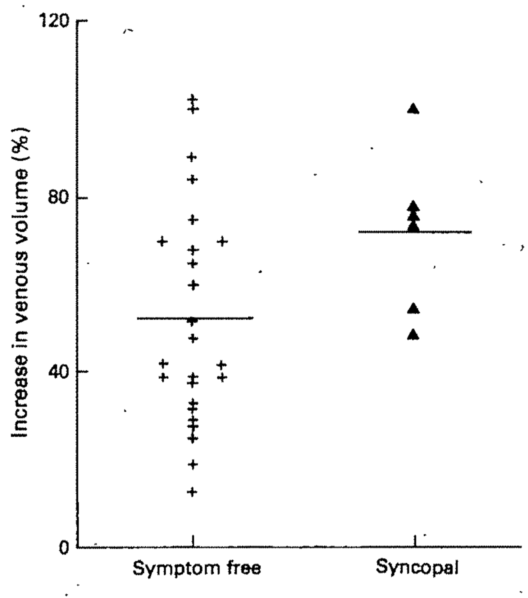
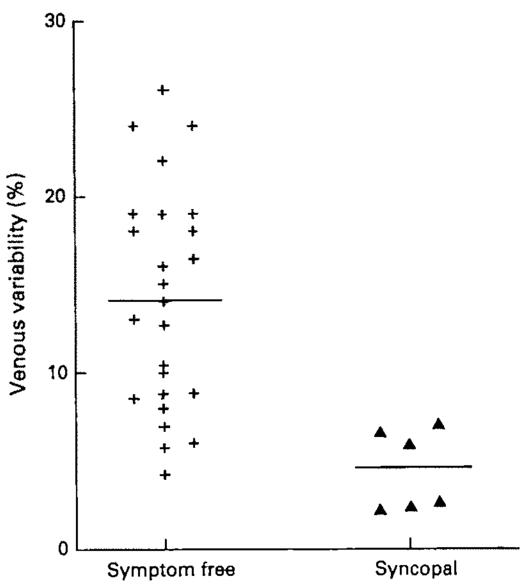


Figure 2 Comparison of percentage increase in venous volume during tilting in symptom free and syncopal patients (scattergram and means; p = 0·05 for difference between means).

Baseline characteristics, mean (SD)

	Symptom free		*With symptoms*
	All *n=25*	*Over 55* *n=13*	*n=6*
Sex (M:W)	15:10	8:5	4:2
Age (y)	56 (17)	70 (7)	66 (6)
Ischaemic heart disease	7	6	1
Vasoactive treatment	8	6	0
Baseline:			
Heart rate (beats/min)	66 (12)	65 (8)	64 (3)
Systolic blood pressure (mm Hg)	138 (27)	155 (21)	142 (15)
Diastolic blood pressure (mm Hg)	78 (11)	84 (9)	75 (8)

Figure 3 Comparison of variability of venous tone during the tilted period in symptom free and syncopal patients (scattergram and means; p = 0·001 for difference between means).



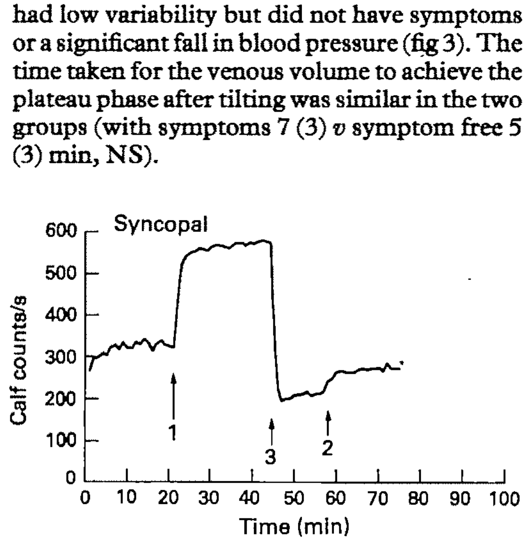
No significant difference in the mean heart rate was recorded at the time of the lowest blood pressure between those with and without symptoms (64 (23) *v* 72 (13) beats/min, NS). Only one patient in our syncopal group developed a profound bradycardia.

No sigificant difference was found in the time taken for the maximum fall in blood pressure to occur between those with and without symptoms (32 (21) *v* 33 (19) min, NS).

VENOUS RESPONSE

Patients with symptoms had a greater percentage increase in venous volume on tilting than symptom free patients (p = 0·05, fig 2) even when analysis was restricted to those of a similar age (with symptoms 72 (18)% *v* older symptom free 41 (17)%, p < 0·01). The variability of the venous reponse was significantly less in those that developed symptoms (p = 0·001, fig 3). The difference remained significant when those under 55 were excluded (with symptoms 4·4 (2·3)% *v* older symptom free 12·3 (6·4)%, p < 0·01. Fig 4 shows an example of a calf time activity curve in a syncopal patient. Patients who had syncope had a large increase in calf venous volume during the tilted phase; the volume varied little but tended to increase gradually. Some patients, however, had low variability but did not have symptoms or a significant fall in blood pressure (fig 3). The time taken for the venous volume to achieve the plateau phase after tilting was similar in the two groups (with symptoms 7 (3) *v* symptom free 5 (3) min, NS).

Figure 4 Time activity curve from a syncopal patient. Arrows 1 and 2 apply as for figure 1 and arrow 3 indicates head down tilt.



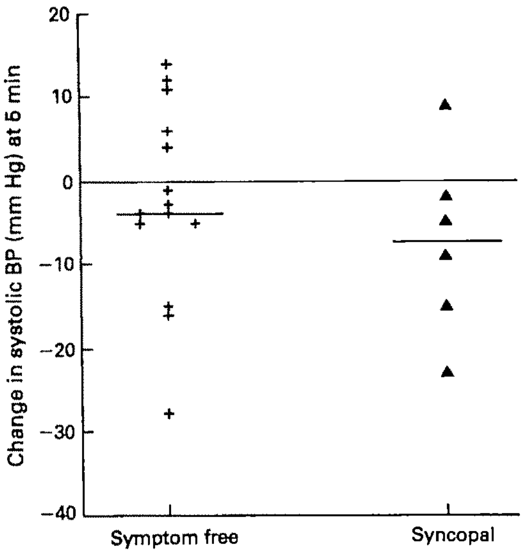


Figure 5 Comparison of fall in systolic blood pressure between horizontal values and recordings made five minutes after tilting in symptom free patients aged over 55 with those from patients with syncope (scattergram and means).

POSTURAL HYPOTENSION

Postural hypotension is judged by a fall in systolic pressure between horizontal and five minutes after tilting. The fall in blood pressure five minutes after tilting was significantly greater in the patients with symptoms, (− 7·5 (11) *v* 2·3 (11), p= 0·05). This difference, however, disappeared when the syncopal patients were compared with the older symptom free patients (fig 5). Of the older subjects tilted, two had a fall in systolic pressure of greater than 20 mm Hg (one symptom free and one with symptoms) and no patient had symptoms at this time.

Discussion

Our study has shown that patients who experience syncope during a head up tilt test have less variable venous tone and tend to have a larger increase in the volume of blood in their calf during tilting. This group of patients, identified by the tilt test, are thought to have malignant vasovagal syndrome. Symptoms induced by postural hypotension were not a problem in these patients. Also, none of the syncopal patients showed autonomic dysfunction when non-invasively tested by the methods of Ewing.[10]

Our evidence suggests that at least some of the pathology in malignant vasovagal syndrome lies in the peripheral veins. During head up tilt roughly 600 ml of blood shifts from the central circulation to the legs.[11] The body normally responds to this movement of blood by activating the sympathetic nervous system. This causes an increase in venous tone that tends to increase the venous return to the heart and maintain the cardiac output when standing. This increase in tone is seen even in an arm vein segment that has been isolated from the circulation by a tourniquet.[12] Other evidence for activation of the sympathetic nervous system lies in the increase in heart rate, peripheral vascular resistance, and plasma noradrenaline concentrations that occur during head up tilt.[13] It is not known if this sympathetic stimulation is set at a constant level or whether it is variable.

Our patients who did not experience syncope had more obvious variability in the volume of calf venous blood, possibly as a result of variable sympathetic stimulation. Perhaps it is important for the calf veins to behave in an active manner with periods of constriction increasing the venous return in response to falling central venous pressure. Indeed we found an inverse correlation between variability of venous tone and the fall in systolic blood pressure during tilting ($r = -0{\cdot}57$, $p < 0{\cdot}01$). It is known that venoconstriction occurs in the arm veins of normal young men when syncope is induced by either head up tilt or negative lower body pressure.[14] When the stimulus became too great for venoconstriction to adequately increase venous return they became syncopal. If patients with malignant vasovagal syndrome have an impaired venous response during tilting this will predispose them to episodes with low central venous pressure and low cardiac volumes. If this occurs in assocation with increased sympathetic drive the conditions are right for stimulation of the Bezold-Jarisch reflex and vasovagal syncope. The importance of adequate sympathetic stimulation is underlined by the work of Almquist *et al* which shows a greatly increased rate of syncope in head up tilt testing when patients had a concomitant infusion of isoproterenol.[6] It is thought that high sympathetic outflow is required to generate the excessive intraventricular pressures that provoke the Bezold-Jarisch reflex.

In our study we found that only 19% of patients had syncope. This proportion is substantially lower than other groups looking at malignant vasovagal syndrome. Fitzpatrick and Sutton have reported that 74% of their patients experienced syncope.[5] Abi-Samra *et al* had a positive response in 42% and Strasberg *et al* detected syncope in 37·5% of their patients.[15 16] In interpreting these figures it is important to remember that the patients we studied had not already had intensive investigation and were relatively unselected. It is likely that these people had a range of conditions responsible for their initial symptoms. This had the advantage of allowing observation of the peripheral venous response in a population ranging from normal to severely abnormal. Our low rate of syncope is partly explained by the 45° of tilt that we used by contrast with the greater stress of 60° that has now become accepted as the optimal degree of tilt.[17] Our symptom free group may contain some people that would be syncopal in response to the greater stress. It was not our purpose to investigate the incidence of syncope but to examine the role of the veins in the pathogenesis.

As expected the fall in blood pressure during tilting was related to increasing age ($r = -0{\cdot}37$, $p < 0{\cdot}05$). This is thought to be due to a gradual functional impairment of the autonomic nervous system.[18] Consequently, it is perhaps predictable that malignant vasovagal syndrome tends to occur in older people.

Two pieces of work have stated that vasovagal syncope was associated in some instances with overactive cardiovascular reflexes.[19 20] This is not necessarily at variance with our findings. In one study the syncopal subjects were young and had no history of syncope. These results may simply reflect a group prone to fainting when under medical investigation and head up tilt. A second study also found evidence of exaggerated cardiovascular reflexes as judged by heart rate response both to tilting and to stimulation of the carotid sinus. Peripheral venous tone was not examined and the exaggerated heart rate response may reflect a normal reflex response to low cardiac filling pressures.

Our chosen method for assessment of calf venous volume has been validated against limb plethysmography.[7] Pharmacological studies suggest that calf venous volume is not influenced by changes in arterial volume. Hydralazine and felodipine cause noticeable decreases in systemic vascular resistance, but no change in venous volume.[8 21] By contrast, nitrates cause a 10% increase in venous volume without causing significant reductions in systemic vascular resistance.[8] Captopril, which acts on arterial and venous beds, decreases systemic vascular resistance and causes venous volume to increase.[22] Our extrapolation from calf measurements to venous volume is therefore not unreasonable, and this technique appears to be ideally suited to monitor changes in peripheral venous volume in response to posture.

We postulate that the abnormality in patients with malignant vasovagal syndrome may lie within the peripheral veins themselves, perhaps involving the smooth muscle or endothelium, and is not the result of generalised dysfunction of the autonomic nervous system. If the primary pathological defect is identified more satisfactory treatment may result—particularly for the vasodepressor type of malignant vasovagal syndrome.

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1 Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983;1:90–102.
2 Come PC, Bertram P. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. *Circulation* 1976;54:624–8.
3 Rosoff MH, Cohen MV. Profound bradycardia after amyl nitrite in patients with a tendency to vasovagal episodes. *Br Heart J* 1986;55:97–100.
4 Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 1972;85:164–73.
5 Fitzpatrick A, Sutton R. Tilting towards a diagnosis in recurrent unexplained syncope. *Lancet* 1989;i:658–60.
6 Almquist A, Goldenberg IF, Milstein S, *et al*. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 1989;320:346–51.
7 Rutlen DL, Wackers FJT, Zaret BL. Radionuclide assessment of peripheral intravascular capacity: a technique to measure intravascular volume changes in the capacitance circulation in man. *Circulation* 1981;64:146–52.
8 Wathen CG, Hannan WJ, Adie CJ, Muir AL. A radionuclide method for the simultaneous study of the effects of drugs on central and peripheral haemodynamics. *Br J Clin Pharmacol* 1983;16:45–50.
9 Callahan RJ, Froelich JW, McKusick KA, Leppo J, Strauss HW. A modified method for the in vivo labeling of red blood cells with Tc-99m: concise communication. *J Nucl*

Med 1982;23:315–8.

10 Ewing DJ. Recent advances in the non invasive investigation of diabetic neuropathy. In: Bannister R, ed. *Autonomic failure. A text of clinical disorders of the autonomic nervous system*. 2nd ed. Oxford: Oxford University Press, 1988: 667–89.

11 Sjostrand T. The regulation of the blood distribution in man. *Acta Physiol Scand* 1952;26:312–27.

12 Page EB, Hickan JB, Sieker HO, McIntosh HD, Pryor WW. Reflex venomotor activity in normal persons and in patients with postural hypotension. *Circulation* 1955;11: 262–70.

13 Grassi G, Gavazzi C, Cesura AM, Picotti GB, Mancia G. Changes in plasma catecholamines in response to reflex modulation of sympathetic vasoconstrictor tone by cardiopulmonary receptors. *Clin Sci* 1985;68:503–10.

14 Epstein SE, Stampfer M, Beiser GD. Role of the capacitance and resistance vessels in vasovagal syncope. *Circulation* 1968;37:524–33.

15 Abi-Samra F, Maloney J, Fouad FM, Castle L. The usefulness of head up tilt testing and haemodynamic investigations in the work up of syncope of unknown origin [Abstract]. *PACE* 1987;10:406.

16 Strasberg B, Rechavia E, Sagie A, *et al*. The head up tilt table test in patients with syncope of unknown origin. *Am Heart J* 1989;118:923–7.

17 Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. *J Am Coll Cardiol* 1991;17:125–30.

18 Smith JJ, Hughes CV, Ptacin MJ, Barney JA, Tristani FE, Ebert TJ. The effect of age on hemodynamic response to graded postural stress in normal man. *J Gerontol* 1987; 42:406–11.

19 Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. *Circulation* 1990;81:1803–10.

20 Wahbha MMAE, Morley CA, Al-Shimma YMH, Hainsworth R. Cardiovascular reflex responses in patients with unexplained syncope. *Clin Sci* 1989;77:547–53.

21 Muir AL, Wathen CG, Hannan WJ. Effects of felodipine on resistance and capacitance vessels in patients with essential hypertension. *Drugs* 1985;29(suppl 2):59–65.

22 Capewell S, Taverner D, Hannan WJ, Muir AL. Acute and chronic arterial and venous affects of captopril in congestive cardiac failure. *BMJ* 1989;299:942–5.

Br Heart J 1992;67:491–7

Short-term and long-term treatment with propafenone: determinants of arrhythmia suppression, persistence of efficacy, arrhythmogenesis, and side effects in patients with symptoms

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Abstract

Objective—To assess the clinical criteria predicting the short and long-term efficacy of propafenone, an agent with class IC antiarrhythmic activity and a broad pharmacological profile.

Designs—Prospective study of propafenone at doses of 450 to 900 mg/day during a six week dose titration period (including a placebo phase with two separate 24 Holter recordings). Responders to treatment were followed for one year.

Patients—One hundred patients with frequent ventricular arrhythmias (>30 extrasystoles/h) of Lown class III and IVA/B and without evidence of myocardial infarction within the past six months.

Analysis—Multivariate regression analysis of spontaneous arrhythmia variability and of different clinical variables to determine the short and long-term efficacy and safety of propafenone.

Measurements and main results—Propafenone 450 mg/day was effective in 30/100 patients (30%), and at 600 mg/day another 14 responded. The efficacy of propafenone correlated with a low spontaneous arrhythmia variability and, as shown by multivariate analysis, with a lower patient age ($p < 0·05$). When the dose was increased to 900 mg/day a further six (12%) patients responded. However, with increasing doses of propafenone, the one year probability of effective treatment decreased from 86% (450 mg/day) to 67% (600 mg/day) and to 44% (900 mg/day). After restudying the patients at three, six, and 12 months and after dose adjustment in 11/44 patients (25%), 31 patients (70%) remained responders. Loss of permanent antiarrhythmic efficacy was best predicted by the initial dose that achieved a response. No patient died suddenly or had arrhythmogenic effects during Holter monitoring. Side effects occurred in 36% of patients but these rarely limited long-term treatment.

Conclusions—A younger age, low spontaneous arrhythmia variability, and particularly a low titration dose were the best predictors of the short and long term efficacy of propafenone. All other responders should have repeated Holter recordings during the first year of treatment.

Propafenone is a potent antiarrhythmic drug and is widely used in Europe and the United States for the management of ventricular arrhythmias.[1-5] It has class IC activity and produces considerable sodium-channel blockade in heart muscles and Purkinje fibres[6-10] with little effect on ventricular repolarisation.[11] Additionally, propafenone produces β adrenergic blockade in vitro[6 9 10 11-13] and in vivo,[14 15] and has weak calcium channel blocking properties.[6 9 10] Short-term, placebo controlled, double blind studies (dose range from 450 to 1200 mg/day) showed suppression of frequent ventricular extrasystoles and of episodes of non-sustained ventricular tachycardia in 60–85% of patients treated with propafenone.[2 5 16 17] Similar results were reported in uncontrolled studies.[3 18-20] The combination of potent sodium channel and β blocking properties are characteristics known to stabilise the electrophysiological properties of myocardial cells.[21] Propafenone is therefore viewed as being of particular interest.[1 22 23]

However, evidence from the Multicenter Cardiac Arrhythmia Suppresion Trial (CAST) of an excess mortality among post-infarction patients treated for ventricular arrhythmias with the class IC drugs encainide and flecainide has called into question the overall benefit of class IC drugs.[24] Because propafenone has similar electrophysiological effects to encainide and flecainide and because information on its long-term effects is incomplete,[25 26] the use of propafenone has also been restricted. At present, it is uncertain whether propafenone can be safely and effectively used for long-term treatment of patients with symptomatic and frequent ventricular arrhythmias, but without recent myocardial infarction.[1]

In a prospective, one year follow up trial, we studied 100 patients with symptoms of frequent ventricular arrhythmias to examine long-term efficacy and safety of propafenone treatment. We used multivariate analysis to predict persistence or loss of long-term efficacy and arrhythmogenic effects related to antiarrhythmic treatment in these patients.

Patients and methods

PATIENT SELECTION

The ethics committee of the University of Freiburg approved the study, which was conducted from December 1987 to November 1989. We studied 100 patients (69 men, 31 women; median (SD) age 62 (6) range 28–78) with frequent ventricular extrasystoles (>30/h) and ventricular pairs or tachycardia who had given informed consent (table). We included only those patients with symptoms of arrhythmia.

Ninety three patients had organic heart disease (for example, diagnosed by exercise testing or echocardiography). Thirty two had had catheterisation of the right or left ventricle.

Exclusion criteria were myocardial infarction within the past six months, presence of myocardial ischaemia during an exercise test before the study (an exercise test was negative in all the patients), heart failure NYHA class IV, sustained ventricular tachycardia (>30 repetitive beats or tachycardia that was not haemodynamically tolerated by the patient), bradycardia <50 beats/min and conduction disturbances of the sinoatrial and atrioventricular nodes, more than second degree bundle branch block, atrial fibrillation, sustained ventricular tachycardia, a baseline QT-interval of >500 ms (Romano-Ward and Jervell-Lange-Nielsen-syndrome), serum potassium <3·0 mmol/l, serum creatine >2 mg/dl, hepatic disease, concomitant medication with other antiarrhythmic agents and calcium channel blocking agents (except nifedipine), and previous treatment with propafenone. Patients taking digoxin were included only if treatment had been started before they entered the study.

STUDY DESIGN

Before entry into the study all patients underwent an initial wash-out period of one week and a qualifying 24 hour Holter monitoring period. The patient was only included in an active treatment group if the first 24 hour Holter examination showed >30 symptomatic ventricular extrasystoles per hour and repetitive ventricular arrhythmias (ventricular pairs or salvos). Baseline examinations (physical examination, electrocardiogram, chemical blood analysis, echocardiogram) were performed at this time. The ejection fraction was determined in all patients by invasive measurements or by echocardiography.

Data on 100 patients before antiarrhythmic treatment

Variable	*Value*
Sex (M:F)	69:31
Age (mean (SD)) (y)	62·7 (6·8)
Underlying heart disease (patients):	
Coronary artery disease	50
Previous MI	(14)
Cardiomyopathy	14
Valve disease	9
Pulmonary heart disease	7
Other heart disease	13
No heart disease	7
NYHA classification (patients):	
NYHA I	33
NYHA II	50
NYHA III	17
NYHA IV	0
Ejection fraction (%) (mean (SD))	41 (8)
Ventricular arrhythmias (patients):	
>30 symptomatic VE/h	100
Lown class III	11
Lown class IVA	35
Lown class IVB	54
VE/24h (mean (SD))	10·875 (6594)
VB/24h (mean (SD))	209 (278)
VT/24h (mean (SD))	26 (46)
Previous antiarrhythmic treatment	18/100

MI, myocardial infarction; NYHA, New York Heart Association; VE, ventricular extrasystole; VB, ventricular pairs; VT, ventricular tachycardia.

All patients underwent a 10 day placebo period with 24 hour Holter recordings on day 3 and day 10. The second Holter recording was used to assess the spontaneous variability of ventricular arrhythmias and to confirm the arrhythmia suppression obtained during active treatment.

All patients included in the active treatment study were treated with propafenone (150 mg three times a day) for one week. If arrhythmia suppression was not effective, the dose of propafenone was increased during a second week to 600 mg/day (300 mg twice a day). The first group of 50 patients was given propafenone (900 mg/day, 300 mg three times a day) in hospital if they did not respond to the lower doses. The criteria for response were those of Morganroth *et al* and Graboys *et al* (a reduction in ventricular extrasystoles of >84%, of ventricular pairs by >90%, and of ventricular tachycardia by 100%).[26-28] Arrhythmogenic events were defined according to the criteria reported by Podrid *et al.*[29] All patients had a weekly electrocardiogram, measurement of plasma drug concentrations, and assessment of side effects.

All patients who were considered to be suitable for long-term treatment with propafenone were studied after three, six, and 12 months of treatment by 24 hour Holter recording, electrocardiogram, plasma drug concentration, and side effects. Non-responders who did not have therapeutic plasma concentrations of propafenone plasma had repeat 24 hour Holter recording two weeks later.

All Holter recordings were analysed semiautomatically by a Cardiodata MK 4 system. The recording time was 24 hours; the Holter recording was repeated in patients who had fewer than 18 hours of registration time that was artefact free. All ventricular tachycardia episodes were displayed and documented. A visual 1:1 analysis for the incidence of arrhythmias was performed blindly in 5% of the tracings by a second investigator. Both the sensitivity and the specificity of the analysis were >98%.

STATISTICAL ANALYSIS

All measurements are reported as median values or, when indicated, as mean +/− SD. Single and partial correlations were analysed by a χ^2 test (including Yates' correction coefficient), Student's t test, and the U test for comparison of median values. Analysis of variance was done by the "repeat-measurement" model for pre and post dose changes. All tests were performed at a two-sided significance level of 0·05. Multivariate regression analysis was used to determine the influence of different clinical variables on the short term efficacy of propafenone.

Results

Propafenone 450–600 mg/day was initially effective in 44/100 patients (44%) enrolled in the study. In 43/44 responders and 23/56 non-responders arrhythmia related symptoms were abolished. After one year 31/44 patients continued to respond to propafenone. None of the patients died suddenly during treatment with propafenone.

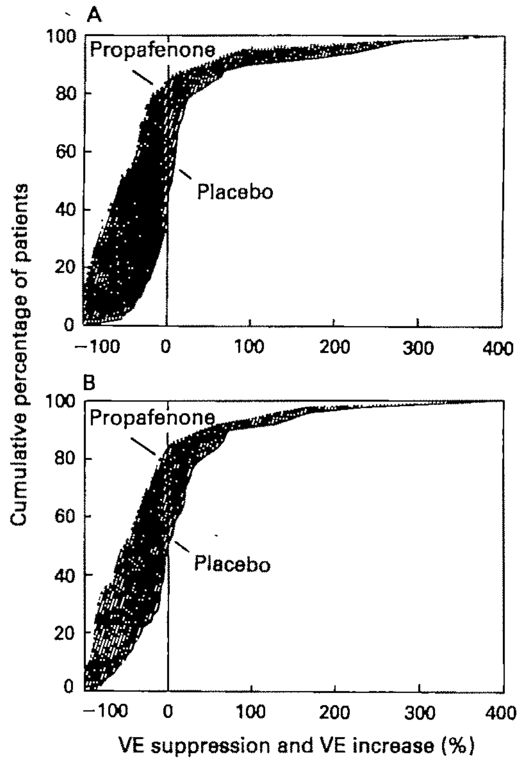

Figure 1 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular extrasystoles (VE) between the first and second placebo 24 h Holter recordings (+400% increase) and during a Holter recording when the patient was treated with propafenone (450 mg/day) (propafenone) in patients with coronary artery disease (A) and those without (B). The shaded area indicates a superior effect of propafenone.

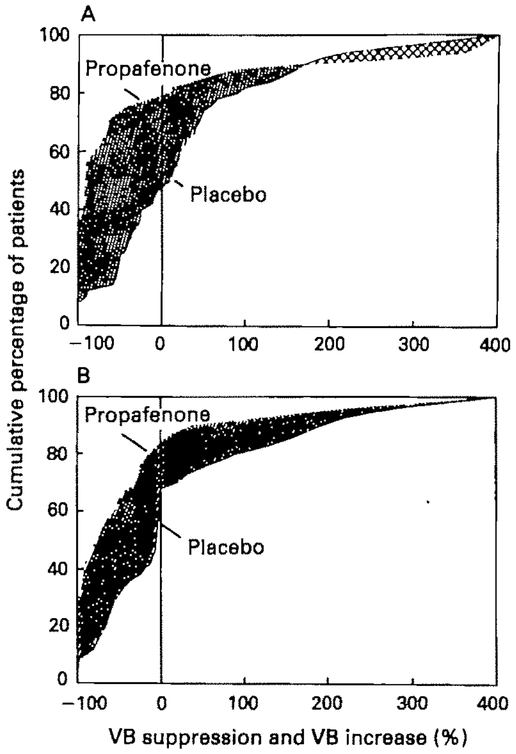

Figure 2 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular pairs (VB) between the first and second placebo 24 h Holter recordings and during a Holter recording made when the patient was treated with propafenone (450 mg/day) in patients with coronary artery disease (A) and those without. The shaded area indicates a superior effect of propafenone and the hatched area indicates a superior effect of placebo.

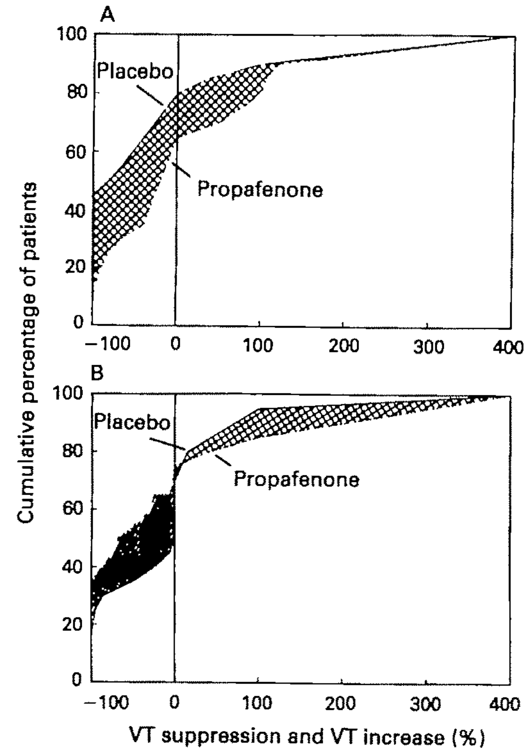

Figure 3 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular tachycardia (VT) between the first and second Holter recordings and during a Holter recording when the patient was treated with propafenone (450 mg/day) in patients with coronary artery disease (A) and those without (B). The shaded area indicates a superior effect of propafenone and the hatched area indicates a superior effect of placebo).

ARRHYTHMIA VARIABILITY DURING THE PLACEBO AND TREATMENT PERIODS

Figures 1–3 reveal spontaneous arrhythmia variability. Examination of Holter recordings during placebo treatment showed that about 50% of patients showed a decrease and 50% an increase in the frequency of single ventricular extrasystoles. In order to assess the effect of the underlying heart disease on the spontaneous variability of arrhythmia we analysed the patients with coronary artery disease separately from those without. There was a clear difference in the spontaneous variability of repetitive arrhythmias. A reduction of 100% or an increase of >100% in the frequency of ventricular pairs or tachycardia after placebo was more common in patients with coronary heart disease (figs 2 and 3).

Spontaneous arrhythmia variability was important when propafenone efficacy was analysed. Figures 1–3 summarise the effects of a daily dose of 450 mg propafenone in all patients. In patients without coronary heart disease 35% had total suppression of ventricular tachycardia after propafenone; however, this was only 18% more than that seen during the placebo period (fig 3B). In patients with coronary artery disease total suppression of ventricular tachycardia was seen in 44% of patients during the placebo period.

During treatment with propafenone this was unexpectedly reduced to 12% (fig 3).

The graphs used in figs 1–3 also allowed us to assess the efficacy of propafenone independently of the criteria used to define a responder. This can be of importance when arrhythmia related symptoms are significantly reduced in individuals who do not fulfil the response criteria. When we examined all the responses to treatment with 450 mg propafenone we found that propafenone had different effects on ventricular extrasystoles, ventricular pairs, and tachycardia (fig 3). For example, in repetitive arrhythmias increased efficacy of propafenone (shown by a leftward shift of the response curve) was often associated with a lowering of the plateau level, indicating that an increasing proportion of patients show some evidence of proarrhythmia at the same time (figs 2 and 3).

Because the spontaneous variability of ventricular arrhythmias was high we used combined criteria (for example >84% reduction of ventricular extrasystoles, a 90% reduction in the frequency of bigeminy, and the complete suppression of ventricular tachycardia) as a measure of the antiarrhythmic efficacy of propafenone. We studied the reliability of these criteria by comparing the initial two placebo Holter recordings that were separated by a week. During the placebo period none of our patients met these criteria.

During treatment with propafenone, the resting heart rate decreased from 74 to 68 beats/min ($p < 0{\cdot}05$), the PR interval increased from 0·15 to 0·22 s ($p < 0{\cdot}05$), and the QRS and QT intervals remained unchanged.

SHORT AND LONG-TERM EFFICACY OF ORAL PROPAFENONE

During dose titration, 44/100 patients (44%) were responders to propafenone (450 mg/day, 30 patients; 600 mg/day, 14 patients). When the dose was increased to 900 mg/day in centre A another six patients (12%) were added to the responder group. The median incidence of ventricular extrasystoles in 24 hours was reduced from 8434 to 2125 in non-responders (median reduction 66%) and from 5642 to 207 in responders (median reduction 96%). Episodes of ventricular pairs were reduced from 65 to seven in non-responders (median reduction 88%) and from 104 to 0 episodes in responders (median reduction 100%). Episodes of ventricular tachycardia over 24 hours were reduced from 6 to one in non-responders and from 4 to 0 episodes in responders. Of the patients responding to 450–600 mg/day propafenone, 43/44 responders and 23/56 non-responders lost their arrhythmia related symptoms after propafenone. In the non-responders loss of symptoms was associated with a significantly higher reduction in the rate of ventricular extrasystoles ($p < 0{\cdot}01$) and a lower Lown class after treatment ($p < 0{\cdot}01$).

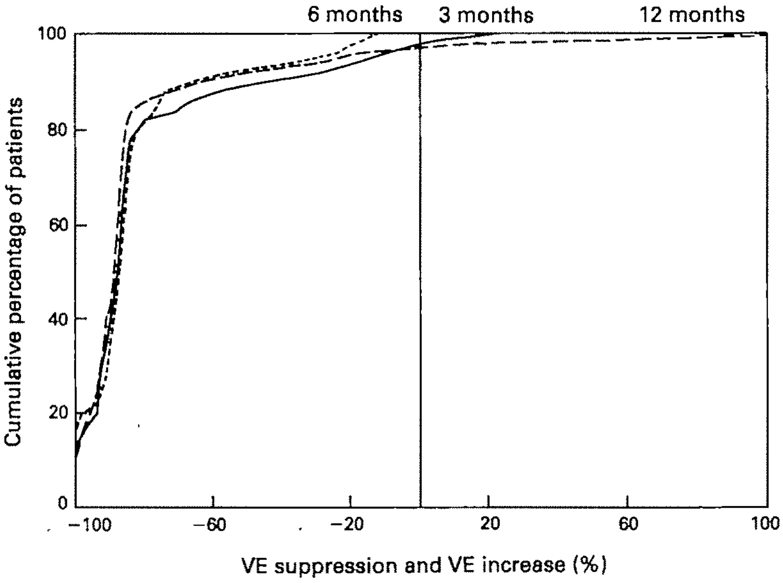

Figure 4 Effect of propafenone on ventricular extrasystoles (VE) after three (closed line), six (solid line), and 12 months (dotted line) of therapy compared with the initial placebo Holter recording (−100% reduction to +100% increase). A total of 44 patients is included initially responded to propafenone 450–600 mg/day (ordinate = 100%).

Multivariate analysis showed a positive correlation between arrhythmia suppression during short-term propafenone therapy and a lower patient age ($p < 0{\cdot}012$), while sex, underlying heart disease, NYHA class, Lown class (IVA, B), concomitant digitalis medication, occurrence of side effects, or presence of coronary heart disease were unrelated to propafenone efficacy.

Thirty eight of the 44 patients (86%) completed a one year follow up while taking 450–600 mg/day; 31 remained as responders (that is, 31% of all patients considered for antiarrhythmic treatment and 74% of all the surviving patients treated long-term). However, 11 of these patients (25%) needed a change of dose after three or six months despite a therapeutic plasma concentration of propafenone. Three of the six patients who did not complete one year follow up required the 900 mg/day dose. The other three patients died from non-sudden and non-cardiac death or in an accident. One patient died from progressive heart failure, one stopped propafenone after carcinoma was diagnosed, and one because of side effects.

Figure 4 shows the response curve for all patients after three, six, and 12 months. In multivariate analysis of the possible predictors of long-term efficacy of the initial propafenone dose we examined all the variables tested for short-term efficacy. Except the titration dose itself, none of these variables was predictive of permanent arrhythmia suppression in the responder group. Though, a permanent response was significantly more likely in patients who initially responded to 450 mg/day (25/29 patients) than in those who responded to 600 mg/daily (8/12, $p < 0{\cdot}01$). At centre A where the dose titration included 900 mg only 4/9 responders continued to take propafenone after one year.

SIDE EFFECTS AFTER SHORT AND LONG-TERM TREATMENT WITH PROPAFENONE

During short term treatment six patients stopped propafenone because of side effects (450 mg/day, two with nausea; 600 mg/day, one with vomiting; 900 mg/day, three with nausea) and two patients because of exacerbation of ventricular extrasystoles (>400% increase). Side effects were reported in a total of 36/100 patients (36%).

During the follow up one patient stopped treatment because of side effects. Ten of 44 patients reported transient side effects during long-term treatment. None of the initial responders to propafenone had arrhythmogenic events during Holter recording.

Discussion

Recent data from the CAST study[24] have fuelled the debate[30–35] on the risk-benefit ratio of the use of agents with class IC antiarrhythmic activity. In the CAST study post-infarction patients who initially responded to flecainide or encainide had a worse outcome during the follow up while taking these drugs than patients taking placebo. This study, however, also raised many unresolved questions about all patients with arrhythmia. First, is the high risk of agents with class IC activity in the CAST study also found in patients without recent myocardial infarction. Second, do patients with more frequent and repetitive arrhythmias (21% of patients in the CAST study) have a better benefit/risk ratio? Third, is repeated Holter monitoring mandatory to detect loss of efficacy and arrhythmogenic effects during long-term treatment in patients who initially responded to treatment? Fourth, how should we treat patients with potentially uncontrollable arrhythmias who required treatment for symptoms after CAST. Fifth, should we expect similar results with other class IC agents, such as propafenone?

Although propafenone shares some of the electrophysiological features of flecainide and encainide it differs from both. It has additional β blocking[3,6,9–13] and calcium-channel blocking properties.[6,9,10] The β blocking dose-related effect was found even at low doses in the study by Härtel[36] and others[13,19] and may enhance the class I properties of propafenone.[21] Placebo studies showed the clinical effectiveness of propafenone,[16] which was as effective as disopyramide,[31,32] quinidine,[33] tocainide,[34] flecainide[35] or even amiodarone in suppressing ventricular arrhythmias.[37] It was no more arrhythmogenic than other agents with class IC activity.[38] Unfortunately, there are few valid long-term studies of propafenone in which Holter monitoring obtained months after the start of treatment could confirm that its antiarrhythmic efficacy persists and that arrhythmogenesis does not increase.[25]

EFFICACY OF PROPAFENONE DURING DOSE TITRATION AND LONG-TERM TREATMENT

The present study aimed to assess long-term efficacy and safety of propafenone in a group of 100 patients with symptomatic ventricular arrhythmias. Patients with recent myocardial infarction were excluded. Therefore our study can not be compared with CAST. Additionally, all our patients had >30 ventricular premature beats, 89% of patients had repetitive ventricular arrhythmias, and all patients clearly had symptoms caused by arrhythmias. As in previous reports, the spontaneous variability during placebo treatment was high in our patients and increased with the complexity of the clinical arrhythmia, especially in patients with coronary artery disease. This variability affected the efficacy of propafenone. Propafenone at a dose of 450 mg/day totally suppressed repetitive ventricular arrhythmias in about 10% of patients; after placebo the proportion of patients with total suppression was three times higher. To eliminate the false positive results established by the two 24 hour Holter recordings after placebo we used combined and restrictive criteria for drug induced suppression of arrhythmia.

We chose to show data on arrhythmia variability, on propafenone efficacy, and on arrhythmogenicity simultaneously and independently of statistical criteria. We used data from the two placebo Holter recordings to assess the spontaneous arrhythmia variability and to create the baseline curve. When we added data on the efficacy of propafenone to this graph, the area between the placebo and propafenone curves showed a complete picture of the antiarrhythmic and proarrhythmic potency of the drug in a particular patient group.

The major aim of the present study was to assess data on the prediction of the long-term efficacy of propafenone treatment. All our patients were given a daily dose of 450–600 mg propafenone which was effective in 44% of patients during a short-term study. These results resemble those reported by others[1,4,16] and those we reported in 100 patients when doses of 450 mg and 750 mg were used and the response rate was 56%.[5] We found that arrhythmia related symptoms disappeared in 41% of patients not classified as responders. However, those non-responders with symptoms and those without were clearly different in terms of the effect on ventricular extrasystoles and suppression of repetitive arrhythmias. It remains uncertain whether these patients who lost their symptoms during treatment but did not meet the criteria for response should continue further treatment. The overall safety of propafenone during this one year observation period favours continuation of treatment at the lowest dose of propafenone that prevents symptoms.

MULTIVARIATE ANALYSIS FOR THE PREDICTION AND THE MAINTENANCE OF THE EFFICACY AND SAFETY OF PROPAFENONE

Multivariate analysis showed that older patients were less likely to respond to propafenone. There were no correlations with other clinical variables. Side effects or acute arrhythmogenesis were not predicted by any of the clinical variables. In the present study the dose was increased to 900 mg/day only in hospital for safety reasons and the increase added another 12% of patients to the responder group. Unfortunately, large studies of the long-term effects of propafenone based on repeat Holter recordings are rare, as are studies of the predictors of long-term efficacy. In our study at the end of one year 70% of patients given long-term treatment and 31% of patients with symptoms remained responders to propafenone. However, the likelihood that propafenone treatment would still be effective after one year decreased as the titration dose increased; thus, it was reduced by >50% when the titration dose was 900 mg/day. Multivariate analysis showed that the titration dose was the variable most predictive of long term propafenone efficacy. Because of the 25% loss of propafenone efficacy during the follow-up, repeat Holter monitoring is mandatory especially in patients with higher titration doses. This is also relevant to the CAST study because with higher doses of class I agents there was a likelihood of >50% that treatment would be ineffective after one year of therapy.

In the CAST study there was considerable interest in mortality and the occurrence of arrhythmogenic events during Holter monitoring in patients treated because they have symptoms. Though our patient group was too small for us to make any definite conclusions, none of our patients died from sudden cardiac death during the one year follow-up, nor did any propafenone responder show arrhythmogenesis during subsequent Holter monitoring. So in our study a placebo group was unlikely to provide more information on this point. In the CAST study, however, a significant number of patients died suddenly after antiarrhythmic therapy.

CLINICAL IMPLICATIONS

This study emphasises the importance of careful assessment of the spontaneous variability of ventricular arrhythmias inherent in a particular group of patients considered for antiarrhythmic treatment. We used a type of graphical analysis which provides an interesting overview of the spontaneous arrhythmia variability and of the antiarrhythmic and arrhythmogenic potency of any antiarrhythmic agent. When propafenone was used in a dose of up to 600 mg in patients with frequent symptomatic arrhythmias, about half of the patients were effectively treated and most of these patients remained responders during one year of follow up. Only the titration dose was a predictor of the persistence of the drug response. Therefore, patients treated by propafenone over longer periods should have repeat Holter monitoring.

1 Oates JA, Wood AJ. Propafenone. *N Engl J Med* 1990; 322:518–25.
2 Salerno DM, Granrud G, Sharkey P, Asinger R, Hodges M. A controlled trial of propafenone for treatment of frequent and repetitive ventricular premature complexes. *Am J Cardiol* 1984;53:77–83.
3 Podrid PJ, Lown B. Propafenone: a new agent for ventricular arrhythmia. *J Am Coll Cardiol* 1984;4:117–25.
4 Harron DWG, Brogden RN. Propafenone. A review of its pharmacokinetic properties, and therapeutic use in the treatment of arrhythmias. *Drugs* 1987;34:617–47.
5 Geibel A, Meinertz T, Zehender M, Vitak J, Hohnloser S, Just H. Antiarrhythmic efficacy and tolerance of oral propafenone in patients with frequent ventricular arrhythmias: Experience of a multicenter study. *Eur Heart J* 1989;10:81–7.
6 Delgado C, Tamargo J, Tejerina T. Electrophysiological effects of propafenone in untreated and propafenone pretreated guinea pig atrial and ventricular muscle fibers. *Br J Pharmacol* 1985;86:765–75.
7 Thompson KA, Iansmith DH; Siddoway LA, Woosley RL, Roden DM. Potent electrophysiologic effects of the major metabolites of propafenone in canine Purkinje fibers. *J Pharmacol Exp Ther* 1988;240:950–5.
8 Malfatto G, Zaza A, Forster M, Sodowick B, Danilo P, Rosen MR. Electrophysiologic, inotropic and antiarrhythmic effects of propafenone, 5-hydroxypropafenone and N-depropylpropafenone. *J Pharmacol Exp Ther* 1988; 246:419–26.
9 Ledda F, Mantelli L, Manzini S, Amerini S, Mugelli A. Electrophysiological and antiarrhythmic properties of propafenone in isolated cardiac preparations. *J Cardiovasc Pharmacol* 1981;3:1162–73.
10 Dukes ID, Vaughan Williams EM. The multiple modes of action of propafenone. *Eur Heart J* 1984;5:115–25.
11 Kohlhardt M. Basic electrophysiologic actions of propafenone in heart muscle. In: Schlepper M, Olsson B, eds. *Cardiac arrhythmias: proceedings of the first international Rythmonorm congress*. New York: Springer Verlag, 1983: 91–101.
12 von Philippsborn G, Gries J, Hofmann HP. Pharmacological studies on propafenone and its metabolite 5-hydroxypropafenone. *Arzneimittelforschung* 1984;34: 1489–97.
13 McLeod AA, Stiles GL, Shand DG. Demonstration of beta adrenoceptor blockade by propafenone hydrochloride: clinical pharmacologic, radioligand binding and adenylate cyclase activation studies. *J Pharmacol Exp Ther* 1984; 228:461–6.
14 Hill MR, Gotz VP, Harman E, McLeod I, Hendeles L. Evaluation of the asthmogenicity of propafenone, a new antiarrhythmic drug: comparison of spirometry with metacholine challenge. *Chest* 1986;90:698–702.
15 Müller-Petzer H, Greger G, Neugebauer G, Hollmann M. Beta-blocking and electrophysiological effects of propafenone in volunteers. *Eur J Clin Pharmacol* 1983;25:831–3.
16 Singh B, Kaplinsky E, Kirsten E, Guerrero J, and the Propafenone Multi-Center Research Group. Effects of propafenone on ventricular arrhythmias: Double-blind, parallel, randomized, placebo-controlled dose-ranging study. *Am Heart J* 1988;116:1542–51.
17 de Soyza N, Terry L, Murphy ML. Effect of propafenone in patients with stable ventricular arrhythmias. *Am Heart J* 1984;108:285–9.
18 Siddoway LA, Thompson KA, McAllister CB. Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences. *Circulation* 1987;75:785–9.
19 Brodsky MA, Allen BJ, Abate D, Henry WL. Propafenone therapy for ventricular tachycardia in the setting of congestive heart failure. *Am Heart J* 1985;110:794–9.
20 Hammill SC, Sorenson PB, Wood DL, *et al*. Propafenone for the treatment of refractory complex ventricular ectopic activity. *Mayo Clin Proc* 1986;61:98–103.
21 Deedwania PC, Olukotun AY, Kupersmith J, Jenkins P, Golden P. Beta blockers in combination with class I antiarrhythmic agents. *Am J Cardiol* 1987;60:21D–6D.
22 Michel D. Propafenone on the way into a new world. *Fortschr Med* 1989;107:81.
23 Vaughan Williams EMV. *Antiarrhythmic agents*. ed. In: Vaughan Williams, ed. Berlin, Heidelberg, New York: Springer Verlag, 1–39.
24 The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.
25 Dinh H, Baker BJ, deSoyza N, Murphy ML. Sustained therapeutic efficacy and safety of oral propafenone for treatment of chronic ventricular arrhythmias: a 2-year experience. *Am Heart J* 1988;115:92–6.
26 Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB. Limitations of routine long-term electrophysiologic monitoring to assess ventricular ectopic frequency. *Circulation* 1978;58: 408–14.
27 Graboys TB, Lown B, Podrid PJ, DeSilva R. Longterm survival of patients with ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol* 1982;50:437–43.
28 Horowitz LN. Ventricular arrhythmias: control of therapy by Holter monitoring. *Eur Heart J* 1989;10:53–60.
29 Podrid PJ. Aggravation of arrhythmia: A complication of antiarrhythmic drug therapy. *Eur Heart J* 1989;10:66–72.
30 Ravid S, Podrid PJ, Novrit B. Safety of longterm propafenone therapy for cardiac arrhythmia—experience with 774 patients. *J Electrophysiol* 1987;1:580–90.
31 Rabkin SW, Boroomand-Rashti K, McKinnon J, Rotem E. Comparison of propafenone and disopyramide in the treatment of ventricular premature complexes: a randomized double blind crossover placebo controlled trial. *Can J Cardiol* 1987;3:105–10.
32 Nacarella F, Brachetti D, Palmieri M, Cantelli I, Bertaccini P, Ambrosioni E. Comparison of propafenone and disopyramide for treatment of chronic ventricular arrhythmias: placebo-controlled, double-blind, randomized crossover study. *Am Heart J* 1985;109: 833–40.
33 Dinh HA, Murphy ML, Baker BJ, deSoyza N, Franciosa JA. Efficacy of propafenone compared with quinidine in chronic ventricular arrhythmias. *Am J Cardiol* 1985; 55:1520–4.
34 Gebhardt A, Schmuderer R, Hilpert P. Vergleichende Untersuchungen von Tocainide und Propafenon zur Behandlung von ventrikulären Arrhythmien. *Arzneimittelforschung* 1984;34:303–6.
35 Klempt HW, Nayebagha A, Febry E. Antiarrhythmische

Wirksamkeit von Mexiletin, Propafenon und Flecainid bei der ventrikulären Extrasystolie: Eine vergleichende Untersuchung bei Patienten mit Zustand nach Herzinfarkt. *Z Kardiol* 1982;71:340–9.

36 Härtel G. Efficacy of oral propafenone in chronic ventricular arrhythmias: a placebo-controlled cross-over exercise study. *Eur Heart J* 1985;6:123–9.

37 Fauchier JP, Cosnay P, Rouesnel P, *et al.* Etude comparative de l'efficacite de la propafenone de la lamiodarone dans le traitement des extrasystoles ventriculaires chroniques. *Arch Mal Coeur* 1986;79:1495–505.

38 Podrid PJ, Lampert S, Graboys TB, Blatt CM, Lown B. Aggravation of arrhythmia by antiarrhythmic drugs: incidence and predictors. *Am J Cardiol* 1987;59:38E–44E.

ABSTRACTS IN CARDIOLOGY

The aortic root in bicuspid aortic values

It is well known that the aortic root at commissural and supra-aortic levels increases in bicuspid aortic stenosis; it is less well known that such root dilation may be instrumental in contributing to aortic regurgitation with bicuspid valves in the absence of any obstruction. What is of interest is that the aortic root is also dilated with functionally normal bicuspid aortic valves. The aortic root abnormality is thus primary and not a mere secondary phenomenon.

M J DAVIES

Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves

Rebecca T Hahn, Mary J Roman, Allen H Mogtader, Richard B Devereux

To determine whether aortic root dilation associated with a bicuspid aortic valve occurs independently of valvular hemodynamic abnormality, aortic root dimensions were measured by two-dimensional echocardiography in 83 adults with a functionally normal (n = 19), mildly regurgitant (n = 26), severely regurgitant (n = 27) or stenotic (n = 11) bicuspid aortic valve and compared with findings in normal subjects matched for age and gender. Aortic root measurements were made at four levels: anulus, sinuses of Valsalva, supraaortic ridge and proximal ascending aorta. Seventy-one percent of patients with a bicuspid aortic valve were men.

When compared with control subjects, all hemodynamic sub-groups showed a significantly larger aortic root size at three levels: sinuses of Valsalva, supraaortic ridge and proximal ascending aorta ($p < 0{\cdot}05$ to $p < 0{\cdot}001$). The prevalence of aortic root enlargement among all hemodynamic subgroups ranged from 9% to 59% at the level of the anulus, 36% to 78% at the sinuses, 47% to 79% at the supraaortic ridge and 50% to 64% in the ascending aorta.

Thus, there is a high prevalence of aortic root enlargement in patients with a bicuspid aortic valve that occurs irrespective of altered hemodynamics or age. These findings support the hypothesis that bicuspid aortic valve and aortic root dilation may reflect a common development defect.

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Br Heart J 1992;67:498–9

CASE REPORTS

Streptokinase treatment of a thrombosed Björk-Shiley prosthesis in the aortic position

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Abstract

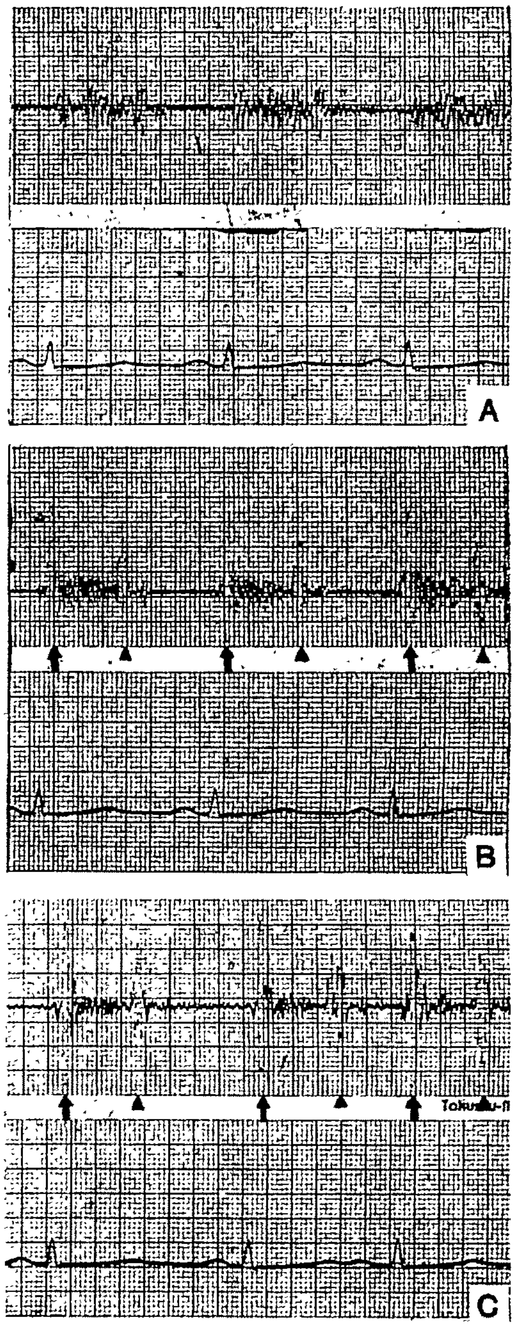
Dysfunction of a mechanical prosthetic valve caused by thrombus formation is usually treated surgically. A patient with a thrombosed Björk-Shiley valve in the aortic position was treated successfully with intravenous streptokinase. The considerable improvement in the patient's clinical condition and the phonocardiographic, echocardiographic, and cinefluoroscopic evidence of normalisation of prosthetic valve function established the efficacy of thrombolytic therapy of a thrombosed prosthetic valve in this patient.

Thrombosis is a major complication of mechanical prosthetic valves, causing valve occlusion or systemic thromboembolism.[1 2] The reported annual incidence of these complications was 5%.[2 3] Surgery is the usual treatment in patients with prosthetic valve dysfunction caused by thrombosis: mortality is high.[2-4] A few attempts to treat thrombosed prosthetic valves with thrombolytic agents have been successful.[5-7] We report here a patient with a thrombosis of a Björk-Shiley prosthesis in the aortic position that responded to thrombolytic therapy.

Case report

A 33 year old man had aortic valve replacement with a 23 mm planoconvex Björk-Shiley valve seven years before and he was adequately anticoagulated with warfarin 2·5 mg daily. He presented with a five day history of exertional dyspnoea (New York Heart Association class II) and reported that he could no longer hear the valve clicks. He had stopped taking warfarin three months before. He had a pulse rate of 100 per minute and a blood pressure when supine of 120/80 mm Hg. There was no evidence of heart failure or endocarditis. No prosthetic valve sounds were heard and a grade 3/6 aortic ejection murmur was present. The prothrombin time by Quick's one stage test was 13/12 seconds.

A cross sectional echocardiogram showed restricted mobility of the prosthetic valve disc with no clots or vegetations. Cinefluoroscopic examination showed that the prosthetic valve disc opened by only 20°. A phonocardiogram obtained with the transducer placed at the "aortic area" in the second right intercostal space parasternally showed an aortic ejection murmur and no prosthetic valve sounds (fig 1A).



Phonocardiograms recorded at the aortic area: (A) on admission, (B) two hours after treatment with streptokinase, and (C) six hours after treatment with streptokinase. The closing sounds (arrow heads) and opening sounds (arrows) of the prosthetic valve are indicated.

The patient was given 1·5 million units of streptokinase intravenously over 30 minutes, followed by an infusion of heparin at the rate of 1000 units per hour for 24 hours to maintain the clotting time at one and a half times his basal clotting time (measured at the start of treatment), and aspirin (150 mg per day). Phonocardiographic recordings were obtained every hour with the microphone placed at the same position.

Two hours after treatment started the patient reported that he could hear faint valve sounds. Physical examination showed a decrease in the aortic ejection murmur and the closing sounds of the prosthetic valve were clearly audible. The phonocardiographic recording confirmed the findings (fig 1B). Six hours later the patient could clearly hear the prosthetic valve sounds "normally". At auscultation sharp opening and closing prosthetic valve sounds and a soft aortic ejection murmur were heard. The phonocardiogram confirmed these findings (fig 1C). A repeat cross sectional echocardiogram showed a normally functioning valve. Cinefluoroscopy showed that the prosthetic valve disc opened to a full 60°. The patient was symptom free on discharge and experienced no complications related to the streptokinase therapy.

At follow up one month later there was no evidence of a recurrence of thrombosis and the phonocardiographic, echocardiographic, and cinefluoroscopic findings remained normal.

Discussion

Although modern prosthetic heart valves are becoming less thrombogenic, thrombotic complications do occur.[2-4]

For aortic prosthetic valves (especially of the Björk-Shiley type) the wide variability of the ratio of the intensity of the opening and closing sounds makes clinical interpretation of this sign inaccurate.[6] Phonocardiography provides one of the most reliable positive indices of a thrombosed prosthesis, especially when a previous phonocardiographic record is available for comparison.[6] Cross sectional echocardiography and cinefluoroscopy are other non-invasive methods of confirming the diagnosis and monitoring the efficacy of thrombolytic therapy.

In this patient the complete absence of prosthetic valve sounds and development of exertional dyspnoea along with his history of not taking anticoagulant therapy pointed strongly to a diagnosis of prosthetic valve thrombosis. Serial phonocardiograms provided an objective index of thrombolysis (figure). Though the patient's symptoms were mild, there was every likelihood of life-threatening valve obstruction or systemic embolisation,[1 6] so urgent intervention was warranted. When thrombolytic treatment is not effective, surgical intervention is indicated. In our patient streptokinase therapy was successful and the patient experienced complete relief of dyspnoea and the return of audible valve sounds. Potential complications of thrombolytic therapy include allergic reactions to streptokinase, haemorrhages owing to the systemic lytic state or systemic thromboembolism caused by loss of adhesion between a partially lysed thrombus and the prosthesis.[8] Our patient experienced no complications of the thrombolytic therapy.

As thrombolytic agents become more potent, safe, and thrombus-specific, the need for surgical intervention for thrombotic complications of prosthetic valves should be reduced.

1 Kloster FE. Diagnosis and management of complications of prosthetic heart valves. *Am J Cardiol* 1975;35:872–85.

2 Brawley RK, Donahoo JS, Gott VL. Current status of the Beall, Björk-Shiley, Braunwald-Cutter, Lillehai-Kaster, and Smellof-Cutter cardiac valve prosthesis. *Am J Cardiol* 1975;35:855–65.

3 Ben-Zvi J, Hildner FJ, Chandraratna PA, Samet P. Thrombosis on Björk-Shiley aortic valve prosthesis. *Am J Cardiol* 1974;34:538–44.

4 Fernandes J, Damel J, Yang SS, *et al.* Late thrombosis of the aortic Björk-Shiley prosthesis. *Chest* 1976;70:12–6.

5 Inberg MV, Havia T, Arstila M. Thrombolytic treatment for thrombotic complications of valve prosthesis after tricuspid valve replacement. *Scand J Thorac Cardiovasc Surgery* 1977;11:195–8.

6 Witchitz S, Veyrat C, Moisson P, Scheinman N, Rozenstajn L, *et al.* Fibrinolytic treatment of thrombus on prosthetic heart valves. *Br Heart J* 1980;44:545–54.

7 Gagnon RM, Beaudet R, Lemire J, *et al.* Streptokinase thrombolysis of a chronically thrombosed mitral prosthetic valve. *Cathet Cardiovasc Diagn* 1984;10:5–10.

8 Kurzrok S, Singh AK, Most AS, Williams DO. Thrombolytic therapy for prosthetic cardiac valve thrombosis. *J Am Coll Cardiol* 1987;9:592–8.

Br Heart J 1992;67:500–1

Infected interventricular Teflon patch: repair and closure of fistula with omentum

Andrew Chatzis, John Pepper, Tom Treasure

Abstract

A pericardiocutaneous fistula five years after repair of a rupture of the ventricular septum was managed by removing all foreign material (Teflon). The resulting defect was repaired with part of the central tendon of the diaphragm and a pedicle of omentum was used to cover the heart. This radical approach was found necessary after other measures, including surgical excision of the fistula, had failed.

Rupture of the myocardium is one of the more common modes of death after infarction.[1 2] It is amenable to repair but requires some form of patch to close the septal defect and material to buttress the sutures in the friable infarcted ventricular myocardium. Teflon felt is commonly used. This operation has increased in Britain in the period 1979 to 1988 from about 50 cases to about 200 cases per year with an overall mortality of 34%. Mortality varied between 26% (1980) and 39% (1987) with no evident trends.[3] The use of foreign material in surgical repair is associated with a risk of persisting infection that is virtually incurable unless the material is completely removed.

Case report

In 1985 a woman aged 53 had an anterior myocardial infarction caused by occlusion of the left anterior descending coronary artery that was complicated by ventricular septal rupture. The septum was repaired with a double Teflon patch that was brought out through the ventriculotomy with two further ribbons of Teflon to buttress the closure, a standard technique.

She remained well for three years but then presented in July 1988 with an abscess inferiorly in the left breast. It was drained by a general surgeon who recognised that the tract went between the ribs. He did not pursue it further but referred the patient back to the cardiothoracic team. A purulent discharge persisted despite antibiotic treatment. A sinogram showed extention deep into the rib cage and in February 1989 the surgeon who performed the original repair re-explored the pericardium through a left thoracotomy, excised the sinus, and established that the Teflon cardiac repair was the source of chronic infection. The sinus started discharging again a few days after the operation. Understanding the significance of the situation, the patient was against further surgery and preferred conservative management with intermittent antibiotics. The chronically discharging sinus was tolerated for two years.

In January 1991 the patient presented with daily rigors, fever, and an intermittently bloody discharge from the sinus. *Staphylococcus epidermidis* was isolated from the blood. A sinogram confirmed a tract reaching the anterior surface of the ventricle. A left ventriculogram excluded ventricular pseudoaneurysm. The right and circumflex coronary arteries were still free from significant disease. The balance of risks and benefits was thought to justify radical surgery. This was offered to the patient and accepted.

She was reoperated on in April 1991. The femoral artery was cannulated, the previous median sternotomy was reopened, and a cardiopulmonary bypass was established using the right atrium for venous drainage. The heart was completely mobilised, all foreign material was removed, and the area irrigated with Betadine solution. This left a 2 × 3 cm ventricular septal defect with fibrosed margins. Part of the central tendon of the diaphragm was used to close the defect, and the ventriculotomy was closed with a continuous prolene suture through secure fibrous tissue. The whole of the greater omentum was mobilised on the right gastroepiploic artery, brought through the diaphragmatic defect, and tacked in position over the anterior and lateral aspect of the heart.

The patient made a good recovery. She is free from fever and there is no discharge from the sinus.

Discussion

The surgical principles in the eradication of chronic infection include removal of all necrotic tissue and foreign material. This is a major problem when prosthetic material forms an integral part of the repair in cardiac and vascular surgery. In this case a radical operation was the only possible solution, more conservative methods having failed.

Tissue flaps can be used to obliterate space and separate planes to prevent recurrence of fistulas. The omentum has proved highly successful in this respect and has been used for many years by Turner-Warwick *et al* in their work in reconstructing organs damaged by pelvic fracture.[4] Several authors have used it as a means of closing bronchopleural fistulas,[5 6 7] aorto-oesophageal fistulas,[8] aortobronchial fistulas,[9] infected vascular grafts,[10 11] and

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recurrent sternal infection.[12 13] The omentum has been used in the pericardium after removal of Teflon felt used to buttress sutures on the surface of the left ventricle.[14] It has been suggested that it should be used prophylactically and this has been described in a series of 50 high risk cases.[15] As two of these patients died of complications possibly related to the use of the omentum, one due to peritonitis, prophylactic use of the omentum hardly seems justified. Its use, however, in established sepsis seems fully merited and the technique of mobilisation for use in cardiothoracic surgery has been well described by Mathisen *et al.*[16]

The omentum has the potential for absorbing bacteria and exudate[17] and is said to have a lipid angiogenic factor.[18] It is well vascularised and can reach virtually anywhere in the chest or abdomen; as such it is a useful adjunct to the treatment of chronic infection and fistulas under various difficult circumstances.[16] As a general policy it seems wise to avoid the use of foreign material and in particular Teflon felt as infection associated with it is resistant to all medical measures.

1 Delborg M, Held P, Swedberg K, Veldin A. Rupture of the myocardium. Occurrence and risk factors. *Br Heart J* 1985;**54**:11–6.

2 Pugsley W, Treasure T. Surgery for acute myocardial infarction; ventricular septal rupture and mitral regurgitation. *Curr Op Cardiol* 1986;1:859–63.

3 UK Cardiac Surgery Register 1979–1988.

4 Turner-Warwick TR, Wynne EJC, Handley-Ashken M. The use of the omental pedicle graft in the repair and reconstruction of the urinary tract. *Br J Surg* 1967; **54**:849–53.

5 Perianayagram WJ, Booshanam MV, Muralidharan S, Jairaj PS, John S. The use of an omental pedicle flap in the closure of bronchopleura fistulae. *Aust N Z J Surg* 1980;**50**:204–6.

6 Iverson LIG, Young JN, Ecker RR, *et al.* Closure of bronchopleural fistulas by an omentum flap. *Am J Surg* 1986;**152**:40–2.

7 Saito H, Tatsuzawa T, Kikkawa H, Hirano M, Sakatoku M. Transpericardial bronchial closure with omentopexy for pneumonectomy bronchopleura fistula. *Ann Thorac Surg* 1989;**47**:312–3.

8 Cosseli JS, Crawford ES. Primary aortoesophageal fistula from aortic aneurysm: successful treatment by use of omental pedicle graft. *J Vasc Surg* 1990;**12**:269–77.

9 Paul DE, Keagy BA. Management of aortobronchial fistula with graft replacement and omentopexy. *Ann Thorac Surg* 1990;**50**:972–4.

10 Cosseli JS, Crawford ES, Williams JW Jr, *et al.* Treatment of postoperative infection of ascending aorta and transverse aortic arch, including the use of viable omentum and muscle flaps. *Ann Thorac Surg* 1990;**50**:868–81.

11 Joyce W, Huddy S, Smith EEJ. Management of an infected graft in the ascending aorta by an omental pedicle graft and irrigation of povidone iodine. *Br Heart J* 1990;**63**:370–1.

12 Belcher P, McLean N, Breach N, Panneth M. Omental transfer in acute and chronic sternotomy wound breakdown. *Thorac Cardiovasc Surg* 1990;**38**:186–91.

13 Colen LB, Huntsman WT, Morain WD. The integrated approach to suppurative mediastinitis; rewiring the sternum over transposed omentum. *Plast Reconstr Surg* 1989;**84**:936–43.

14 Bluett M, Bolling SF, Kirsh M. Management of recurrent ventricular pseudoaneurysm. *Tex Heart Inst J* 1991; **18**:69–71.

15 Liotta DS, Frank LG. Routine application of the omental pedicle graft. *Tex Heart Inst J* 1991;**18**:8–12.

16 Mathisen DJ, Grillo HC, Vlahakes GJ, Daggett WM. The omentum in the management of complicated cardiovascular problems. *J Thorac Cardiovasc Surg* 1988; **95**:677–84.

17 Turner-Warwick R. The use of the omental pedicle graft in urinary tracy reconstruction. *J Urol* 1976;**116**:341–7.

18 Goldsmith HS, Griffith AL, Kupferman A, Catsimpoolas N. Lipid angiogenic factor from omentum. *JAMA* 1984; **252**:2034–6.

Br Heart J 1992;67:502–3

Subaortic stenosis caused by an unusual fibrous blood-filled cyst of the left ventricle with outflow tract obstruction associated with a ventricular septal defect

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Abstract

A large blood-filled cyst formed from a fibrous tissue tag of a right ventricular septal aneurysm was successfully resected. This cyst, which was causing subaortic stenosis, was attached to the margin of the closed ventricular septal defect and not to the mitral valve itself nor the papillary muscle of the left ventricle.

Left ventricular outflow tract obstruction is often associated with anomalies of the mitral valve apparatus. It almost always originates from the papillary muscle or the mitral valve itself.[1 2] We report a patient in whom the obstructive lesion was an unusual blood-filled cyst formed from a fibrous tissue tag of right ventricular septal aneurysm. This case reminded us that anomalies of both the right and left atrioventricular valve tissue anomalies can cause obstructive lesions.[3]

Case report

The patient weighed 3350 g at birth after an uneventful delivery. When he was three months old a systolic murmur and dextrocardia were noted. Echocardiography performed then and a year and a half later showed a perimembranous ventricular septal defect. The second echocardiographic examination also showed anomalous membranous tissue attached to the membranous portion of the left ventricle. Cross sectional echocardiography performed when the patient was seven years old showed that the ventricular septal defect was closed by a septal aneurysm, and a balloon shaped mass that was 18 mm in diameter with an echolucent centre in the left ventricular outflow tract. Cardiac catheterisation and left ventriculography were performed. Angiography showed that the large cyst moved to the subaortic portion during systole and a pressure gradient of 65 mm Hg across the cyst (fig 1). An electrocardiogram showed sinus rhythm, an axis of +100%, and evidence of left ventricular hypertrophy. Echocardiographic examination showed a wall thickness of 7 mm. The chest x ray showed a cardiothoracic ratio of 52%. At operation right ventriculotomy showed a ventricular septal aneurysm. The septal aneurysm communicated with the left ventricle via a small orifice. The communication was closed after the membranous septal aneurysm was resected. Subsequent aortotomy showed a large smooth, white, round fibrous cyst occupying the entire diameter of the left ventricular outflow tract and attached to the tissue between the perimembranous portion and ventricular septum, which was partly connected to the fibrous tissue that communicated with the ventricular septal aneurysm. It was thought that this fibrous cyst was associated with the septal aneurysm of the right ventricle and dependent on the mitral apparatus (fig 2). This round fibrous cyst (20 mm in diameter) was filled with blood. During the resection the blood escaped through a small orifice. The postoperative course was smooth and postoperative cardiac catheterisation showed neither a ventricular communication nor a pressure gradient from the left ventricular outflow tract to the ventricular apex. Macroscopic examination confirmed that the cyst was composed of white, elastic fibrous and gelatinous tissue. Histological examination showed that the cyst wall was made of mucus and degenerated fibrous tissue but not cardiac muscle fibre; these components were identical to those in the ventricular septal aneurysm resected from the right ventricle.

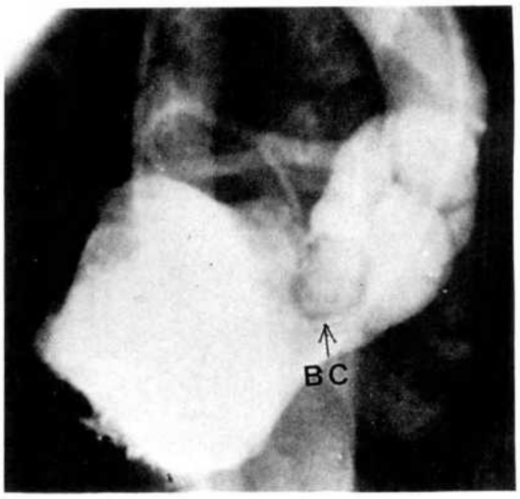

Figure 1 Left ventriculogram showing a large blood-filled cyst in the subaortic portion of the left ventricular outflow tract. BC, blood-filled cyst.

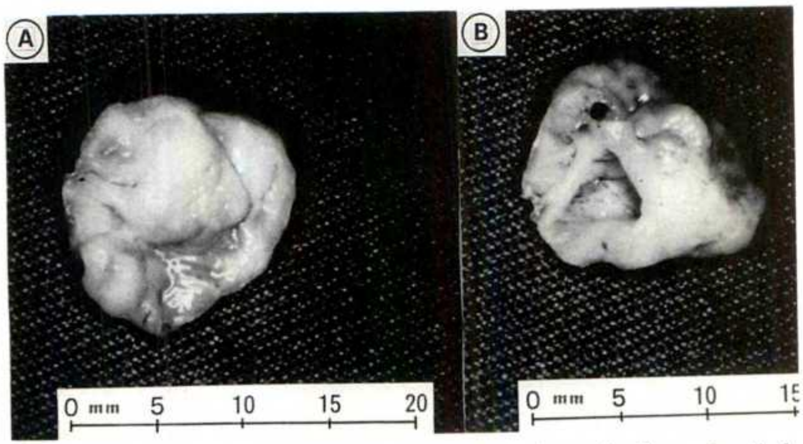

Figure 2 Cyst after removal through the aorta. (A) It had a small orifice at the apical side of the ventricle. (B) The aortic view shows the smooth surface. The wall was 2·0 mm thick.

Discussion

There are several reports of obstruction of the left ventricular outflow tract by a blood-filled cyst attached to the mitral apparatus, by a bleb on the mitral valve, or by accessory tissue from the mitral valve.[2-4] In our patient, however, the cyst was neither a simple blood-filled cyst that had entrapped blood in the mitral valve apparatus nor a mitral bleb that obstructed the left ventricular outflow tract. Investigation during surgery confirmed that there was no connection between the fibrous cyst and either the mitral valve leaflets or the chordae tendineae of the mitral valve. This fibrous blood-filled cyst seemed to have originated and grown from the fibrous tissue tag of an aneurysm of the ventricular septum or from the accessory tissue of the tricuspid valve that had herniated through the ventricular septal defect during the course of closure of the ventricular septal defect.[3] The small posterior orifice in the cyst accords with the hypothesis that the cyst became enlarged by filling up with blood under systolic pressure.[4] The cyst became spherical as blood became trapped in its cavity. However, this blood was discharged through an orifice in the cyst after it was removed. Andersen proposed that maturational closure of a perimembranous ventricular septal defect and obstruction of the left ventricular outflow tract are the mechanisms by which a fibrous diaphragm, fibrous muscular tunnel, anomalous insertion of the atrioventricular valve, or aneurysmal fibrous tag develop.[5] A fibrous tag could have protruded into the left ventricular cavity when the right ventricular pressure rose. Cross sectional echocardiography is essential to confirm that this type of blood-filled cyst showing unusual echolucent mass[6] and attachment can be resected without mitral valve replacement.

We thank Dr S Hiraishi and Dr Y Agata for interpreting the echocardiograms.

1 Hauser AM, Rathod L, McGill J, Rosenberg BF, Gordon S, Timmis GC. Blood cyst of the papillary muscle. *Am J Cardiol* 1983;**51**:612–3.
2 Leatherman L, Leachman RD, Hallman GL, Cooley DA. Cyst of mitral valve. *Am J Cardiol* 1968;**21**:428–30.
3 Sellers RD, Lillehei CW, Edwards JE. Subaortic stenosis caused by anomalies of atrioventricular valves. *J Thorac Cardiovasc Surg* 1964;**48**:289–302.
4 MacLean LD, Culligan JA, Kane DJ. Subaortic stenosis due to accessory tissue on the mitral valve. *J Thorac Cardiovasc Surg* 1963;**45**:382–8.
5 Anderson RH, Lennox CC, Zuberbuhler JR. Mechanisms of closure of perimembranous ventricular septal defect. *Am J Cardiol* 1983;**52**:341–5.
6 Arnold I, Hubner PJB, Firmin RK. Blood filled cyst of the papillary muscle of the mitral valve producing severe left ventricular outflow tract obstruction. *Br Heart J* 1990; **63**:132–3.

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Cardiac rupture after thrombolytic therapy: the use of aprotinin to reduce blood loss after surgical repair

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Abstract

Emergency cardiac surgery after recent thrombolytic therapy is associated with increased blood loss. A patient underwent emergency repair of a ruptured left ventricle after intravenous streptokinase treatment for acute coronary occlusion. High dose aprotinin was given during the operation to reduce the expected blood loss. Surgical repair was successful without bleeding complications. Total postoperative blood loss was 365 ml.

Myocardial rupture is a well recognised and frequently fatal complication of acute myocardial infarction. The effect of thrombolytic therapy on the incidence of myocardial rupture is not yet known. Although emergency surgery offers the only realistic hope of survival,[1 2] it is often difficult to control bleeding from the friable, recently infarcted myocardium.[3] Furthermore, recent administration of thrombolytic treatment has been shown to increase substantially perioperative haemorrhage during emergency cardiac surgery.[4] The protease inhibitor aprotinin (Trasylol: Bayer, Germany) has been shown to reduce the blood loss and use of blood products in patients undergoing cardiopulmonary bypass.[5] We describe a patient who underwent emergency surgery for myocardial rupture after thrombolysis and to whom aprotinin was given with a view to reducing the expected excessive blood loss.

Case report

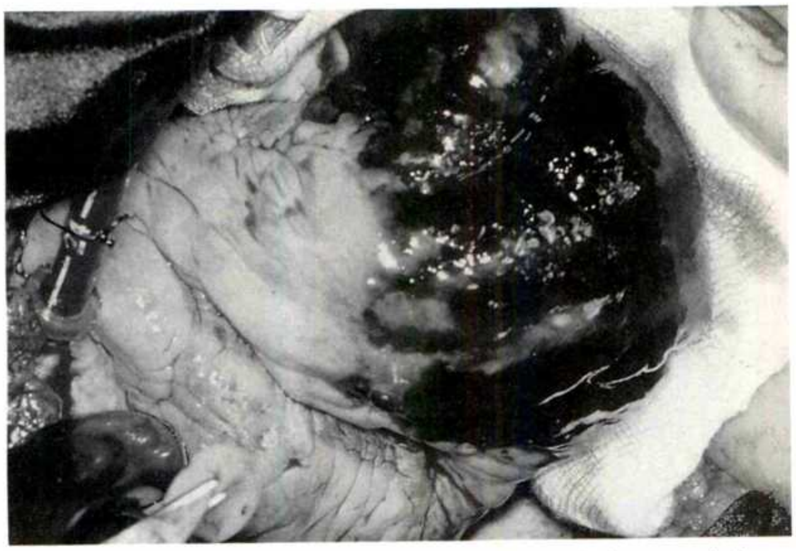
A 67 year old previously fit woman was admitted to the Leeds General Infirmary with a three hour history of chest pain and electrocardiographic evidence of acute anterior myocardial infarction. Treatment with intravenous streptokinase ($1{\cdot}5 \times 10^6$ iu over 30 minutes), heparin, nitrates, and aspirin initially led to relief of her symptoms and resolution of the electrocardiographic changes. One hour later, however, she developed recurrent chest pain associated with new ST changes on the electrocardiogram and developed clinical evidence of cardiogenic shock. Her haemodynamic condition was at this stage improved by inotropic support with dobutamine and counterpulsation with an intra-aortic balloon pump (IABP).

Emergency coronary angiography showed a 90% stenosis in the midportion of the left anterior descending coronary artery (LAD) and although this was successfully dilated by angioplasty, she remained in cardiogenic shock. At this stage pericardial tamponade secondary to myocardial rupture was suspected and was confirmed by transthoracic echocardiography. The patient was transferred directly from the angio suite to theatre for emergency operation. Because of recent thrombolytic therapy, excess perioperative blood loss was expected. The table shows the results of her preoperative coagulation tests. On the basis of these it was decided to administer the protease inhibitor, aprotinin. After induction of anaesthesia, a loading dose of 500 000 kallikrein inactivator units (KIU) of aprotinin was given over 10 minutes, followed by 200 000 KIU per hour until the administration of protamine and the end of the operation.

After sternotomy a large amount of unclotted blood was evacuated from the pericardium with immediate improvement in the haemodynamic state. Inspection of the heart showed an extensive haemorrhagic anteroapical infarct covered with clot, beneath which there was a slit like rupture of the left ventricle (figure). After cardiopulmonary bypass was started necrotic muscle was excised and the ventricular defect repaired. Bypass was stopped with the help of the IABP and dobutamine support, but with otherwise satisfactory haemodynamic recovery. After reversal of heparin with protamine the wound bed, including the raw muscular surface of the ventricular repair, rapidly dried up. Postoperative blood loss from the chest drains was 265 ml for the first 12 hours with a total loss of 365 ml over 24 hours, after which the drains were removed. Over the next few days the patient was gradually weaned from the intra-aortic balloon pump and off inotropic support. She made a good recovery, was discharged home 15 days after operation and was symptom free at follow up after two months.

Results of preoperative coagulation studies, after streptokinase administration

Prothrombin time	25/15
Activated partial thromboplastin time	75/35
Fibrinogen	0·5 g/l
Fibrinogen degradation products	2·0–4·0 mg/l (reference <0·5 mg/l)



Appearance of the heart at operation, showing extensive haemorrhagic anteroapical infarction.

Discussion

Cardiac rupture is a catastrophic event that occurs in about 2%–4% of patients admitted to hospital with an acute myocardial infarction,[1 2] although its incidence is probably under reported. It is not yet known what effect thrombolytic therapy has on the occurrence of myocardial rupture. Preliminary data from the ISIS-II trial showed that 30 patients receiving streptokinase died from cardiac rupture compared with 18 in the control group. Although the differences are not statistically different, there is some evidence that thrombolysis increases the risk of rupture on the first day and decreases the risk on subsequent days.[6] Because treatment and monitoring of patients with acute myocardial infarction is becoming more intensive, it is to be expected that an early diagnosis will be made in a higher percentage of patients suffering cardiac rupture, and this will lead to more patients being presented for emergency surgery. It is likely that, with the widespread use of thrombolytic therapy for acute infarction, many of these patients will come to surgery with a high risk of bleeding. These points are all well illustrated in the present case report.

The beneficial effects of the protease inhibitor aprotinin in reducing blood loss in open heart surgery are now widely known. Although its mechanism of action is not yet completely understood two potential mechanisms of action have been postulated: firstly that it has a protective effect on platelet function, which is normally reduced during cardiopulmonary bypass[7] or secondly that it has an antifibrinolytic effect through its anti-plasmin activity.[8] The reduction in bleeding induced by thrombolytic therapy in the present case lends support to the second of these theories.

Research into the exact mechanism of action of aprotinin is continuing and its clinical applications in both cardiac and non-cardiac surgery are continually being extended. This case illustrates a further indication for the use of aprotinin in reducing the potential complications associated with emergency cardiac surgery after thrombolysis.

1 Fenely MP, Chang VP, O'Rourke MF. Myocardial rupture after acute myocardial infarction: Ten year review. *Br Heart J* 1983;**49**:550–6.

2 Pohjola-Sintonen, Miller JE, Stone PH, *et al*. Ventricular septal and free wall rupture complicating acute myocardial infarction: experience in the multicentre investigation of limitation of infarct size. *Am Heart J* 1989;**117**:809–16.

3 McMullan MH, Kilgore TL, Dear HD, Hindman SH. Sudden blow out rupture of the myocardium after infarction: urgent management. *J Thorac Cardiovasc Surg* 1985;**89**:259–63.

4 Kay P, Ahmad A, Floten S, Starr A. Emergency coronary artery bypass surgery after intracoronary thrombolysis for evolving myocardial infarction. *Br Heart J* 1985;**53**:260–4.

5 Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose Aprotinin (Trasylol). *J Thorac Cardiovasc Surg* 1989;**97**:364–72.

6 Julian DG. Causes of early mortality: rupture and arrhythmia. In: Chamberlain DA, Julian DG, Sleight P, eds. *The management of acute myocardial ischaemia*. London: Chapman and Hall, 1990:84–86.

7 Van Oeveren W, Hander MP, Roozendaal KJ, Eijsman L, Widevuur CRH. Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. *J Thoracic Cardiovasc Surg* 1990;**99**:788–97.

8 Clozel J-P, Banken L, Roux S. Aprotinin: an antidote for recombinant tissue type plasminogen activator (rt-PA) active in vivo. *J Am Coll Cardiol* 1990;**16**:507–10.

Br Heart J 1992;67:506

PLANTS IN CARDIOLOGY

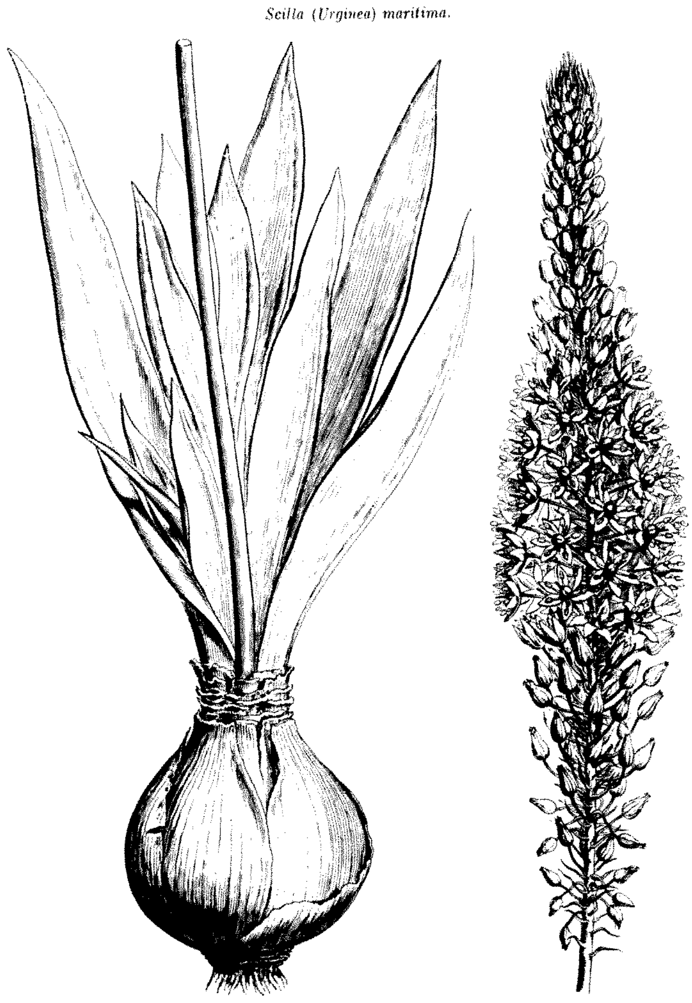

Scilla (Urginea) maritima.

Fig. 501. Base de la plante.

Fig. 502. Inflorescence.

Drimia maritima (L.) Stearn. Baillon H. *Histoire des plantes*, volume 12. Paris: Librairie Hachette, 1892:454.

The Linnean Society

Medicinal plant discovery

Plants are the origin of important cardiovascular drugs and the articles in this series, which now comes to an end, describe their discovery and development. The organic chemicals in plants that we exploit for medical use are often poisonous secondary compounds —that is, not involved in metabolism. So it is not entirely clear why they are produced. Some of them act as defences against animal or insect predators, or indeed against other plants.

In many cases a medicinal plant was first used in folk medicine and with some of these remedies the drug is actually contained in the plant and can be used without modification, as with digoxin and morphine. But in other instances scientific endeavour has been all important in developing new medicines or new uses from the folk remedy. As examples of new medicines one can cite amiodarone, verapamil, and aspirin; while new uses include atropine, reserpine, and ryanodine. There have been important contributions too from other sources. Veterinary medicine led to oral anticoagulants and to an animal model for pulmonary hypertension. Academic chemistry produced lignocaine and it was a patient's own experience that gave us quinidine. There is no obvious explanation for the distribution of medicinal compounds in the plant kingdom. There are about 300 families of plants and just 22 are the source of all the major pharmaceutical drugs. The family Apocynaceae with a total of 2100 species has three that yield important medicines while Compositae with 21 000 species includes only two minor ones.

There must be more plant medicines awaiting discovery, but how do we go about finding them? I do not believe that theorising from existing knowledge will be the answer. Progress is likely to develop along the lines it has followed in the past.

Squill or sea onion *Drimia maritima* (Liliaceae) a Mediterranean plant has been used since antiquity to treat heart disease. It was known to the ancient Egyptians, to Pythagorus (who wrote a treatise on it in the 6th century BC), and to Hippocrates who prescribed it as a diuretic. From Greek and Roman times onward it was widely used as an expectorant, diuretic, and emetic. It was also valued as a rat poison and used to control outbreaks of plague in Egypt. Squill was a constituent of the famous Guy's Pill which remained in the pharmacopoeia until 1960. The active principle is the cardiac glycoside proscillaridin A.

I would like to express my warm thanks to Jane Dawson whose idea it was to produce this series and to Dr Dennis Krikler for his support and encouragement. It has been a pleasure to write these articles and I hope you have enjoyed reading them. Fare-well!

The idea for this series comes from a booklet, *Cardiology from Nature*, which Dr Hollman wrote for Telectonics Pacing Systems at the suggestion of Mr Peter Sedgwick.

The articles are now published as a book, *Plants in Cardiology*, at £5·95 (including postage and packing) available from the BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9JR or from all medical bookshops including the BMJ Bookshop at BMA House.

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Br Heart J 1992;67:507–8

BRITISH CARDIAC SOCIETY NEWSLETTER

Academic meetings

The Society has had its first academic meeting in Fitzroy Square. As readers will know, a teach-in on molecular biology—arranged by Professor David Weatherall—took place on 31 March. We were privileged to have such an auspicious start to a series that we anticipate will become a feature of the Society. Most of those who attended have taken the trouble to write letters of appreciation—an unusual accolade from busy cardiologists. The demand for places was, however, somewhat less than we had anticipated and all who applied were accommodated within our limited space. Many who had wanted to attend were unable to do so because of clinical commitments, and also (we were told) because of contractual obligations. Will consultants' contracts become another powerful hindrance to the maintenance of standards of excellence? We hope not, but we are fearful. Perhaps we should abandon our "members only" rule for teach-ins and for the (forthcoming) workshops to allow more junior trainees to share the benefits. Were this to be the case would members be happy to subsidise the travel arrangements and provide excellent free lunches which are benefits offered at present? Stricter budgetary constraints may well be appropriate whilst maintaining a measure of support. We suggest a compromise with a policy of "members first" for bookings, but with uncommitted places open to non-members a few weeks before the event. The next meeting we have planned should arouse great interest. Michael Davies will arrange a teach-in with the title "New Concepts in the Pathogenesis of Atherosclerosis". The date will be Tuesday 10 November. No-one can claim to be familiar with the new concepts, because by November more progress will surely be known to the cognoscenti in an area that moves with breathtaking speed. You can book now (if you are a member) . . ..

Society staff

The Society is becoming ever more busy. Apart from Council we have 7 active committees, 5 affiliated groups which are likely to make increasing use of the facilities at Fitzroy Square, currently 2 working parties, large databases at the University of Sussex, and active involvement in many areas including an increasing liaison with the media. To manage these disparate interests we have a small dedicated staff comprising only an executive officer, an assistant administrator and book keeper, a part time secretary, and a part time graduate assistant for database entry and management. If the Society is to be efficient in all these areas we need more staff and this policy is being pursued. We hope to recruit a new senior administrator who will work with our executive officer and oversee the full range of our operations. We need another full time secretary, perhaps shared with one of the other new occupants of our house. More will be written on this when plans have been approved or modified by Council.

Society officers and council

Some important changes are already well known. The Society has elected John Parker as President Elect, and we look forward to the first Surgical President in less than a year from now. The field was strong and voting understandably close, but all will be pleased that conspicuous service to the Society over many years has been recognised. John Cleland—the new Assistant Secretary—takes on a burden which will become ever greater with the increasing activities of the Society. Roger Boyle adds to the strength of District General Hospital cardiologists on Council. Many will see this as correcting an imbalance that has caused some comment in recent times.

Affiliated Groups

Changes have also occurred in Affiliated Groups. Huon Gray has taken over from Peter Hubner as Secretary of the British Cardiovascular Intervention Society. To his predecessor, Peter Hubner, goes much credit for the notable influence of BCIS in our specialty. In particular, Peter worked with exemplary patience and determination in the collection of data on cardiac interventions from 1988 onwards. This is not an easy task but audit is important to all, not least to the cardiologists who have chosen to work in an area for which guidelines are yet not fully agreed. We omitted to mention that the President of the British Nuclear Cardiology Group changed in January; it is now Steve Walton. The post rotates each year, and in future we will try to keep up to date.

Working Party: DGH cardiology

The Working Party on Cardiology in the District General Hospital, chaired by Andrew McLeod, has now been completed and will start work soon. The members are: Mahendra Varma, Roger Boyle, Ian Findlay, George Green, Jane Flint, Michael Martin, John Sanderson, Richard Wray, Nick Brooks (representing cardiac centres), and Robin Sadler (representing general practice). Any members with suggestions for topics that should be addressed may wish to contact one of the members of the working party. This can be done either directly or—if members find it easier—through the Society Office. Those who are interesting in making suggestions may find it helpful to look at the previous report that was published in the British Heart Journal in November 1987 (58:537).

Electrophysiology

We have concerns about the future of electrophysiology in the United Kingdom. Our anxiety has been expressed in a letter addressed to Duncan Nichol at the Department of Health, signed by Brian Pentecost representing the Cardiology Committee of the Royal College of Physicians, by Richard Sutton for the British Pacing and Electrophysiology Group, and by one of us for the Society. It addressed the present lack of stretegic planning for the development of major clinical services. Previously, new needs could be discussed with regional health authorities. This was not always satisfactory for a national perspective, but initiatives relating to supraregional services complemented the usual planning arrangements. In the current climate some regions believe that all new developments should be discussed with potential purchasers, but this is not an appropriate way to develop a service that needs national coordination for a sensible distribution of units with adequate funding and appropriately trained staff. The combination of great need, the potential for effective and often curative treatment, and the necessity for both highly specialised skill and dedicated facilities make a powerful case for a new method of strategic planning, and within a priority suggested in *Health of the Nation*. We need a programme of capital investment in the existing major electrophysiology units to increase their scope and efficiency, coupled with a planned development of new units phased over several years with the ultimate aim of one centre in each region.

Busy cardiologists

A health district without a trained cardiologist is unlikely to provide a reasonably comprehensive service appropriate to the 1990s. But the deprivation may not be apparent to general practitioners or to patients who are not fully aware of the potential benefits of modern cardiology. The situation is different in districts that do have a cardiologist, but a workload that is unmanageable. The need is recognised but cannot readily be met. This is likely to be the uncomfortable situation in large districts with only one physician trained in the specialty, especially as he or she is likely to have general medical commitments as well. We have conducted a survey of cardiologists who have single handed responsibility for districts with a population of more than 250,000. We hope this will provide useful ammunition in our struggle to achieve adequate staffing levels. A total of 45 of our colleagues are in this situation. Unfortunately some have been so busy that they have not yet completed their questionnaires, but they will forgive us for pursuing them. It is an excellent cause.

Senior registrars absent for GIM training

Some of our cardiac centres find major difficulties in adhering to the current guidelines of the Specialist Advisory Committee that one year of senior registrar training must be in general internal medicine. They are left without a valuable member of the service team and the service can suffer greatly. The pretence that senior registrars are supernumerary for training alone is unrealistic, unworkable, and even undesirable. The centres often face the problem that no locums are available with suitable training. For some there may be a solution that could be considered, though funding has to be available. One of us has recently spent four fascinating weeks in South Africa. In Capetown (Groote Schuur Hospital) there are a number of excellent and well trained senior registrars some of whom would be glad of an opportunity to spend time in Europe. There will be others in different universities and, perhaps, not only in South Africa. Would it be useful for the British Cardiac Society to help arrange such placements where the excellence of overseas trainees can be guaranteed by trusted contacts? Please write if you have views.

New resuscitation guidelines

We had insufficient space in the May Newsletter to mention the meeting of the American Heart Association for new guidelines in resuscitation. This took place in Dallas in March. Your President was an invited speaker and co-chairman of a session on

International cooperation. Cooperation is of special importance now that we have a European Resuscitation Council. By chance on this occasion, but perhaps by design in future, both the new American and the new European guidelines will be announced almost simultaneously (November 1992) respectively in JAMA and at Resuscitation '92 which is the ERC meeting to be held in Brighton on 20 and 21 November. Delegate registration packages are available from the Society.

Other meetings

We have a number of other meetings to draw to your attention. First, the "3èmes Journées Européennes de la Société Française de Cardiologie" that will take place in Paris on 14–16 January 1993. We have attended this meeting and been impressed by the determination to make it European. Simultaneous translation is available, for example, in the main auditorium. The deadline for the submission of abstracts is 15 July. We can provide abstract forms and additional information. We have also been asked to draw to your attention the Congreso Iberoamericano de Cardiologia, to be held in La Rábida (Huelve, Spain) on 6–10 October. Abstracts may be needed by mid June. We can provide more information.

Prevention in medical education

John Goodwin has written as Chairman of the National Forum for Coronary Heart Disease Prevention: "A new report entitled 'Coronary Heart Disease Prevention in Undergraduate Medical Education' has recently been published by the National Forum for Coronary Heart Disease Prevention, in association with the British Heart Foundation. The report follows a meeting attended by delegates from cardiology, public health and general practice, from medical schools throughout the United Kingdom. It was chaired by Desmond Julian and the President of the British Cardiac Society. A survey of medical schools revealed wide variations in the commitment and time devoted to teaching students about prevention issues. One third of respondents from departments of medicine, including cardiology, indicated that examination questions on the prevention of coronary heart disease were never set. The majority of respondents, however, saw a need for change. The report points to considerable scope for improvement, provided an integrated approach is coordinated throughout training. It recommends that teaching on prevention should be part of clinical cardiology teaching. The whole hospital and medical school environment should support prevention. A research officer, funded by the British Heart Foundation, has recently been appointed by the National Forum to work with medical schools to develop guidelines and resources to improve teaching. The report has been sent to all United Kingdom medical schools and to the General Medical Council. Further copies are available from the National Forum for Coronary Heart Disease Prevention, Hamilton House, Mabledon Place, London WC1H 9TX (£5)."

Proposed British Association of Cardiac Rehabilitation

Hugh Bethall has also written to us: "The provision of cardiac rehabilitation in the United Kingdom has grown enormously over the past 10 years. This growth has been haphazard depending upon local enthusiasts with little overall planning or guidance. Recently a great boost to rehabilitation has been provided by a funding initiative from the British Heart Foundation and the Chest Heart and Stroke Association. There is now a need for an organisation to provide a forum for the professionals of many disciplines who are involved in cardiac rehabilitation. The inaugural meeting of the British Association of Cardiac Rehabilitation will be held at St Catherine's College, Oxford, on Saturday 26 September. Topics to be discussed will be education for rehabilitators, fund-raising, liaison with other national rehabilitation organisations, and the functions and structure of the new Association. The proposed Association will be multi-disciplinary. Several members of the British Cardiac Society are on the steering committee, and it is hoped that cardiologists will be well represented at this meeting. Application forms can be obtained from: Action Heart, Wellesley House, 117 Wellington Road, Dudley, West Midlands DY1 1UB."

News of colleagues

We propose to provide a paragraph on news of colleagues. In future this will include announcements of appointments and retirements. But we end this newsletter on a sad note by recording the death of James Fleming who went to Sheffield from Barts a little over 20 years ago.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
DUNCAN DYMOND
Secretary, British Cardiac Society
9 Fitzroy Square,
London W1P 5AH

NOTICE

Third European Meeting of the French Society of Cardiology

Palais des Congrès, Paris, France, 14–16 January, 1993.

Information and call for abstracts:
S.C.F.
15, rue de Madrid
75008 PARIS, France
Phone: 33 1/43 87 95 14
Fax: 33 1/43 87 17 14

Registration:
Albine Conseil
16 boulevard du Parc
92200 NEUILLY/SEINE, France
Phone: 33 1/47 47 57 37
Fax: 33 1/46 40 70 36

Deadline for abstract submission:
15 July, 1992.

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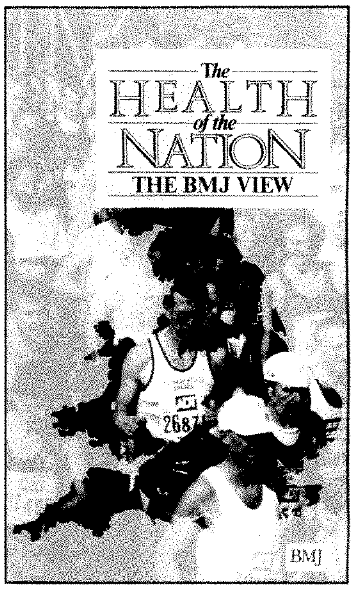
Essential reading

THE HEALTH OF THE NATION: THE BMJ VIEW

EDITED BY RICHARD SMITH, EDITOR OF THE BMJ



". . . a strategy imposed by the government which takes no heed of the views of those who will have to implement it . . . is valueless".

So writes William Waldegrave, Secretary of State for Health, in his introduction to *The Health of the Nation*, the government's consultative document that sets out a strategy for improving the health of the English. Taking Mr Waldegrave at his word on wanting to listen to everybody, the *BMJ* commissioned a series of articles that explain the views of some of those most concerned. Contributors discuss each of the 16 key areas defined in the strategy and suggest other subjects that might qualify as key areas. One article, from the Radical Statistics Health Group, is strongly critical of the strategy; others are critical of various aspects of it, but almost all of the contributors support the idea of setting targets for improving health. Originally published in the *BMJ*, this collection of articles is an important contribution to the debate on how to achieve health for the nation. Furthermore, the articles will be useful beyond the borders of England because most developed countries are now setting strategies to improve health.

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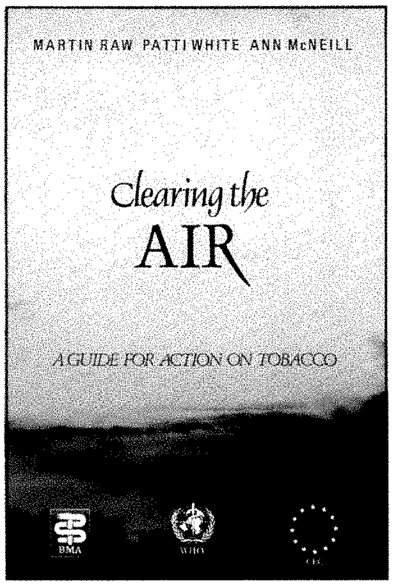
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This practical guide provides an innovative approach to the analysis of tobacco control initiatives, resulting from cooperation between the British Medical Association, World Health Organization, Commission of the European Communities.

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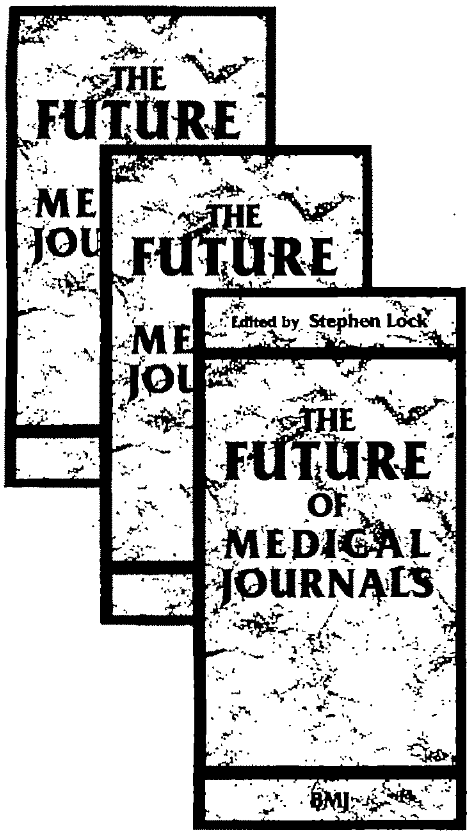

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The debate was lively and the opinions conflicting and forcefully expressed when, to mark its 150 year past, the *BMJ* decided to join with other general medical journals in examining their perhaps not too certain future. At a conference at Leeds Castle editors of major general medical journals throughout the world, with experts in information science, sociology, and epidemiology, discussed the functions and effectiveness of modern journals, and debated possible choices for development. Edited by Stephen Lock, *The Future of Medical Journals* is a unique compilation of papers on this important but little analysed aspect of medical science.

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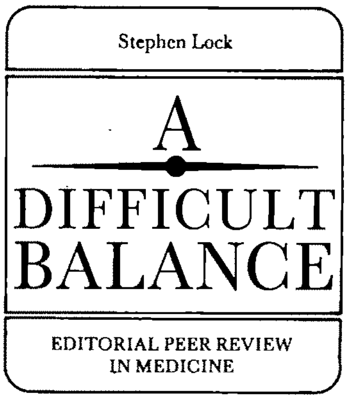

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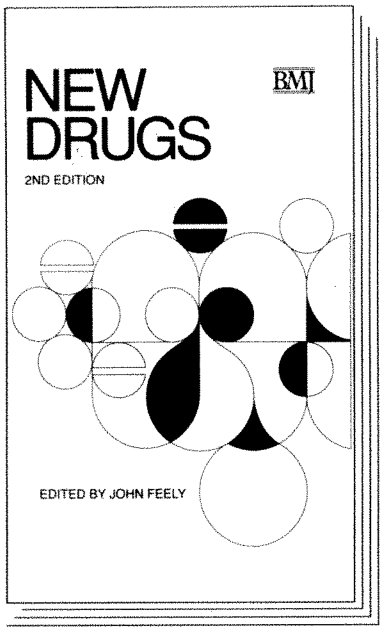

New drugs are continually being developed and knowledge about existing drugs is constantly expanding, so it is essential, but difficult, for doctors to keep up to date with the latest developments. *New Drugs* describes the most important therapeutic advances of the past decade and discusses the drugs that will be in common use in the 1990s. Completely revised and updated, this second edition has been expanded to include 11 additional chapters. Its coverage of practical aspects of drug use, avoidance of adverse reactions and interactions, and prescribing at extremes of age makes it an invaluable guide for busy practitioners who want to get the best out of the new drugs currently available.

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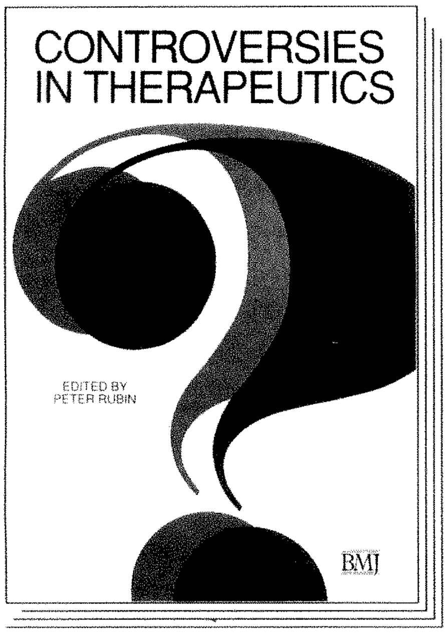

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Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

REFERENCES: 1. Caruana M, Lahiri A, Cashman P, *et al.* Am J Cardiol 1988; **62:** 755-759. **2.** Dickstein K, J Cardiovasc Pharmacol 1987; **9**(Suppl 3): S73-S81.

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